

Evaluation of Co-Segregation Between Bipolar Mood Disorder and Heterozygous Beta-Thalassemia in Patients Originated From Iran

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Abstract: Bipolar affective diseases are relatively common affecting about 1-5% of the population worldwide with heritability about 80%. Previous studies supposed the association of heterozygous β -thalassemia and Bipolar Disorder (BPD). This study examined this association in Iranian patients. A case-control study recruited 110 patients with BP and 118 subjects with no psychiatric disorders. Total Cell Blood Count (CBC) was undertaken for all subjects. Haemoglobin electrophoresis was only carried out for those who were microcytic in the blood picture (MCV<75 FL). Ten percent of patients and 10.1% of control group were microcytic in their CBC. Haemoglobin electrophoresis revealed 9 out of 110 (8.18%) in patients and 5 out of 118 (4.24%) in control group had haemoglobin A2 elevated between 3.4-7% and identified as minor β -Thalassemia. In the present case-control study, no significant linkage was identified comparing the prevalence of heterozygous β -thalassemia in two groups. Based on the results presented here, we could not conclude any association between BPD and heterozygous β -thalassemia.

Key words: Bipolar affective disorder, β -thalassemia, co-segregation, Mazandaran

INTRODUCTION

The genetic basis of bipolar disorder (BPD), with heritability about 80% remains unclear to date because of phenotypic heterogeneity despite of intensive investigation (Payne *et al.*, 2005). Bipolar affective diseases are relatively common, affecting about 1 to 5% of the population worldwide (Kennedy *et al.*, 2003; Smith *et al.*, 2005).

Although the molecular DNA markers are now available, but because of uncertainty of the major loci involve in bipolar disorder, different diseases such as G6PD deficiency and β -thalassemia were used as phenotypic markers in linkage studies (Kelsoe *et al.*, 1993; McQuillin *et al.*, 1999; Bocchetta, 2005).

The co-segregation between BPD and thalassaemia was first aroused when Joffe and colleagues reported BPD coupled with heterozygote thalassemia in three persons of one family (Joffe *et al.*, 1986). Interaction between mood disorders of the bipolar spectrum and β -thalassemia then were reported from both case and population studies (Harada *et al.*, 1995; Brett and Dunn, 1998; Bocchetta, 2005). Bocchetta *et al.* (2005) recently noticed that blood disorder in schizoaffective patients is more prevalent

than other mood disorders and conclude that heterozygous β -thalassaemia might play a role as a susceptibility factor in bipolar spectrum disorders in specific populations (Bocchetta, 2005).

The gene frequency of β -thalassemia is as high as 10% in Mazandaran, the northern province of Iran (Najmabadi *et al.*, 2001). A survey of bipolar spectrum disorders among subjects with an established diagnosis of heterozygous β -thalassemia from high prevalence areas was recommended in previous study (Bocchetta, 2005). This study was designed to examine the co-segregation between heterozygous β -thalassemia and BPD in the patients originated from Mazandaran, the Northern province of Iran.

MATERIALS AND METHODS

Subjects: In this case-control study, 110 patients with bipolar disorder were selected from inpatients and outpatients of Zareh Psychiatry Hospital, in Sari. They had a documented diagnosis of BPD according to DSM-IV. The control group included 118 subjects whom were randomly selected from three university hospitals in Sari at the same period of time. Patients were hospitalised in

psychiatry and haematology wards and all bleeding diseases and anaemic patients were excluded from the study. Because BPD is not prevalent in people over 50 years old or over, the efforts were made to recruit people with 50 years or over as control individuals. The 118 controls had neither BPD history in the past or present, nor the least vulnerability to BPD. Individuals with positive history of BPD, Manic-Depressive Disorder (MDD) or any other psychosis in the first degree relative were also excluded from the control group. In addition, the individual was excluded from the study in both case or control groups, if any uncertainty about inclusion or exclusion criteria happened.

Haematological analysis: Total Cell Blood Count (CBC) was undertaken for all subjects. Haemoglobin electrophoresis was only carried out for those who were microcytic in the blood picture (MCV<75 FL). Individuals with A₂ between 3.4-7% were considered as minor thalassemia with more than 90% certainty (Rund *et al.*, 1992; Behrman *et al.*, 2004).

Statistical analyses: Statistical analyses were carried out using descriptive, least square and odds ratio statistical methods.

RESULTS AND DISCUSSION

One hundred and ten patients with BPD and 118 subjects with no psychiatric disorders were recruited in the case and control groups, respectively. The mean age for the patients was 36.5, while it was 63.5 years for the control group respectively. In total, 31 (28%) and 6 (5.5%) out of 110 patients in the case group had positive family history of mood disorder and psychiatric disorder in the first-degree relatives, respectively (Table 1). These conditions were not observed in the control group. Eleven out of 110 (10%) patients in the case and 12 out of 118 (10.1%) individuals from control group were microcytic in their CBC (MCV<75 fl). Haemoglobin electrophoresis revealed that 9 out of 110 (8.18%) patients in case and 5 out of 118 (4.24%) subjects in the control group had haemoglobin A₂ elevated between 3.4 to 7% and identified as minor β -Thalassemia.

Co-occurrence of β -thalassemic trait and BPD was reported in different studies to date (Bocchetta, 2005), but the controversy is remains as some other studies reported no linkage between thalassemia and BPD (McQuillin *et al.*, 1999; Klar, 2004). The correlations between the two diseases were questioned by Singh and Maguire (1988) when a brother and sister both had BPD but only one had thalassemia. In other study, Bocchetta and Del Zompo (1990) reported the same prevalence of thalassemia and BPD in general population.

Table 1: Minor Thalassemia in patients with bipolar and control group. One hundred and ten bipolar patients and 118 normal controls were tested

	Thalassemia trait	Normal	Total
Bipolar	9	101	110
Normal	5	113	118
Total	14	214	228

$X^2 = 0.928$, $p = 0.335$, Odd ratio = 2.014, 95% Confidence interval = 0.653-6.20

The beta-globin gene, responsible for beta-thalassemia, is located on the short arm of chromosome 11, 11p15. Beta-thalassemia is one of the most common monogenic diseases worldwide. It was proposed that gene(s) located on short arm of chromosome 11 (11 p) might be involved in BPD. For instance, Dopamine D4 Receptor (DRD4) and Tyrosine Hydroxylase (TH) genes (has role in synthesis of catecholamine) and are located on the short arm of chromosome 11, have been extensively investigated in bipolar disorder (Muglia *et al.*, 2002). In further study, a multipoint analysis between bipolar disorder and 13 markers on chromosome 11 including the D2 dopamine receptor failed to reveal any evidence of linkage (Kelsoe *et al.*, 1993). In addition, different genome-wide linkage scans in bipolar disorder, which candidate significant linkage association among different chromosomal regions and BPD, did not showed linkage between BPD and chromosome 11 p (Segurado *et al.*, 2003; Payne *et al.*, 2005; Tomas *et al.*, 2006; Consortium, 2007).

One of the latest genome-wide association studies of 14,000 cases and 3,000 shared controls suggest no association between chromosome 11p and BPD (Consortium, 2007). The strongest signal in BPD was with rs420259 at chromosome 16p12 instead.

CONCLUSION

In the present case-control study, no significant linkage was identified comparing the prevalence of heterozygous beta-thalassemia in 2 groups. There was also not significant difference between the 10% prevalence of heterozygous β -thalassemia in BPD patients and in the general population ($X^2 = 0.928$, OR= 2.014, 95% CI = 0.653-6.20, $p = 0.335$). This result did not show any increased prevalence of heterozygous β -thalassemia among bipolar patients. Based on the results presented here, we could not conclude any association between BPD and heterozygous β -thalassemia.

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