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Clinical study

Association of MIF and MBL2 gene polymorphisms with attempted suicide in patients diagnosed with schizophrenia or bipolar disorder

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ABSTRACT

The aim of this study to investigate the genetic polymorphisms in macrophage inhibitory factor (MIF) and mannose-binding lectin 2 (MBL2) gene in schizophrenia (SCZ) or bipolar disorder (BD) patients with attempted suicide by comparing with a non-attempted SCZ or BD patients and healthy controls. A sample of 108 patients with SCZ, 100 patients with BD and 100 healthy volunteers were included in the study. SCID-I was used to confirm the diagnosis according to DSM-IV-TR criteria. The patients were evaluated by data forms that included sociodemographic, suicidal behavior and symptom severity information. PCR-RFLP was used to determine MIF and MBL2 gene polymorphisms from DNA material. Our results demonstrated that the distributions of MBL2 genotype (AA, AB, BB), combined genotype (AA, AB/BB) and the allele frequencies (A, B) of attempted suicide patients in SCZ were statistically significantly different from the non-attempted SCZ patients. The distributions of the MBL2 genotype (-AA, AB, BB) of attempted suicide patients in SCZ were statistically significantly different from the control group. The distributions of MIF genotype (GG, GC, CC), combined genotype (GG, GC/CC) and the allele frequencies (G, C) of attempted suicide patients in BD were statistically significantly different from the non-attempted BD patients or control group. In summary MBL2 gene polymorphism may be associated with attempted suicide in SCZ and MIF gene polymorphism might be associated with attempted suicide in BD. However, further studies with other gene variants in different ethnic populations are needed to address the exact role of these polymorphisms in SCZ or BD.

1. Introduction

Schizophrenia (SCZ) is a severe psychiatric disorder that can cause significant impairments in psychosocial function, have a chronic course and are seen in around 1% of the general population [1]. The prevalence of lifetime suicide attempts in those with SCZ ranges from 20% to 40%. It was estimated that one in every 20 individuals with SCZ will commit suicide [2]. Bipolar disorder (BD) is a psychiatric disorder which is characterized by manic, depressive and mixed episodes, cause significant impairments in psychosocial and occupational function during episodes [3]. It has been estimated that the risk of suicide in patients with BD to be 20–30 times higher than the population [4]. Lifetime suicide attempts and completed suicides are estimated to range from 25 to 50 % and 8–19% in BD [5].

Epidemiological studies have reported that the risk for suicidal behavior (SB) is heritable, with the currently about 40%. This heritability depends on two main factors. The first factor is an association with psychiatric disorders, the secondly SB is inherited independently [6]. At the same time, a certain genetic predisposition has not been understood yet. Numerous meta-analyses of case-control studies have shown a strong association of genetic polymorphisms with SBs variants in solute carrier family 6 member 4 (SLC6A4) or 5-HTT gene-linked polymorphic region (5-HTTLPR), catechol-O-methyltransferase (COMT) -rs4680, tryptophan hydroxylase 1 (TPH1) -rs1800532-, brain-derived neurotrophic factor (BDNF) -rs6265- and its receptor (NTRK2) are also promising candidates [7]. Besides, recent studies reported aberrant cytokine levels in the blood, cerebrospinal fluid, and postmortem

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brain samples from suicidal completers. For instance, increased blood levels of tumor necrosis factor (TNF-α) and interleukin 6 (IL-6) are associated with suicidal ideation and attempt [8]. Pandey et al. published that post-mortem brain tissue from teenage suicide victims had increased messenger ribonucleic acid (mRNA) and protein levels of TNF-α, IL-1β and IL-6 in certain cortical regions [9]. However, monitoring only cytokine levels of serum and cerebrospinal fluid (CSF) and disregarding the confounding factors (presence of concomitant autoimmune disease, an infection during the measurement of samples) can be misleading without considering the inflammation-related genes.

The Macrophage Inhibitory Factor (MIF) gene is localized to the q11.23 region on chromosome 22. MIF is a cytokine that is responsible for both the innate and acquired immune response. It carries the features of a strong proinflammatory cytokine and may lead to a chronification of diseases [10]. MIF has also been shown to facilitate the deoxyribonucleic acid (DNA) damage response and cell cycle regulation and is related with the hypothalamic–pituitary–adrenal (HPA) axis [11]. Especially as a dysregulation of the HPA axis is hypothesized to play an important pathophysiological role in psychiatric disorders [12]. Again Mannose-binding lectin 2 (MBL2) is an acute-phase protein that plays an important role in the innate immune response. MBL2 is the only collectin that activates the lectin pathway, which is a third pathway different from the classical and alternative pathways of the complement system. It binds to microorganisms, acts as an opsonin, facilitates phagocytosis and activates macrophages. MBL2 is encoded by the MBL2 gene, which consists of 4 exons in the q11.2-q21 region of the long arm of chromosome 10 [13]. When the literature is reviewed, there is no study examining the relationship between SB and MBL2 gene variants. Again apart from a study examining the relationship between completed suicide and MIF gene polymorphism in the Japanese population [14], there is no study examining the relationship between attempted suicide and MIF gene variant in SCZ or BD. Therefore to our knowledge, this is the first study that has examined the relationship between MIF and MBL2 gene variant and attempted suicide in SCZ or BD. The aim of this study is to investigate the relationship between MIF gene and MBL2 gene variant and attempted suicide patient diagnosed with SCZ or BD.

2. Methods

2.1. Patient Selection

A sample of 108 patients with SCZ, 100 patients with BD was followed at Bakirkoy Mazhar Osman Mental Health and Neurology Training and Research Hospital in the period of January-June 2018; additionally, 100 healthy volunteers were included in the study, which was designed as a case-control study. The study was approved by the Local Committee of Bakirkoy Mazhar Osman Mental Health and Neurology Training and Research Hospital (81/07.11.2017).

2.1.1. Diagnostic tools and scales

The participants were informed in detail about the purpose, method and procedures of the study, and their written consent was obtained. The interview was started by filling out data forms that included sociodemographic and clinical information. At the outpatient policlinic interview, it was asked whether they attempted suicide. If they mentioned that attempted suicide, it was learned which method they used. Afterward, the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) was used to confirm the diagnosis according to DSM-IV-TR criteria, and the presence of any psychiatric diagnosis as a basis for exclusion from the study in the healthy control group [15,16]. The Young Mania Rating Scale (YMRS) [17,18], the Hamilton Depression Rating Scale (HAM-D) [19,20] were administered to patients with BD to evaluate the severity of manic or depressive symptoms, to measure of positive symptoms, negative symptoms and general psychopathology in psychotic patients the Positive and Negative Symptoms Scale (PANSS) [21,22] were administered to patients with SCZ.

2.2. DNA isolation and genotyping analyses

Blood samples were obtained from participants at the Istanbul Faculty of Medicine Laboratory of Medical Biology to isolate their deoxyribonucleic acid (DNA) material using the GeneMark Plus Blood Genomic DNA Purification Kit. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used to determine codon 54 A/B (gly54asp) variation in exon 1 of the MBL2 gene and MIF gene − 173 G/C polymorphism [23]. 10% of the sample was randomly selected and the method was controlled on this sample.

2.3. Statistical analyses

Statistical analysis was performed using IBM SPSS version 21.0 (IBM Corp. released 2012; Armonk, NY, USA). Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, percentage. Pearson chi-square test or Fisher's exact test was used to comparing discrete variables, and Bonferroni correction was used in pairwise comparisons to determine which group or groups showed statistically significant results. Statistical significance was accepted as $p < 0.05$ for the results of all analyses.

3. Results

When we look at the percentages of SB, 32.4% (n:35) of the SCZ patients (n = 108; 27 female/81 male) and 30% (n:30) of the BD patients (n = 100; 60 female/40 male) have attempted suicide. The method and type of SB were evaluated on Table 1. The scale scores of the patients diagnosed with SCZ or BD are shown on Table 2.

When the MBL2 (AA, AB, BB) genotype, combined genotype (grouping by considering the presence of mutation allele) (AA, AB/BB) (homozygosis normal, heterozygosis/homozygosis mutant) and the allele frequencies (A, B) of attempted suicide patients with SCZ were compared with the non-attempted SCZ patients, the MBL2 (AA, AB, BB) genotype ($p = 0.026$), (AA, AB/BB) combined genotype ($p = 0.007$) and the allele frequencies (A, B) ($p = 0.003$) distribution of attempted suicide patients with SCZ was found to be significantly different from the non-attempted SCZ patients. The percentage of the genotypes with mutation allele (AB/BB) and mutation allele (B) was found to be statistically higher in the attempted suicide SCZ patients than non-attempted SCZ patients (Table 3). Again when the MBL2 (AA, AB, BB) genotype, combined genotype (AA, AB/BB) and the allele frequencies (A, B) of attempted suicide patients with SCZ were compared with the control group, the MBL2 (AA, AB, BB) genotype ($p = 0.012$) distribution of attempted suicide patients with SCZ was found to be significantly different from the control group (Table 4). When the MIF (GG, GC, CC) genotype, combined genotype (grouping by considering the presence of mutation allele) (GG, GC/CC) (homozygosis normal, heterozygosis/homozygosis mutant) and the allele frequencies (G, C) of attempted suicide patients with SCZ were compared with the non-attempted SCZ patients or the control group, there wasn't found to be significantly difference between the groups ($p > 0.05$) (Data not shown).

When the MIF (GG, GC, CC) genotype, combined genotype (GG, GC/CC) and the allele frequencies (G, C) of attempted suicide

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Table 1
Sociodemographic Characteristics and Suicidal Behavior of Patients.

		Schizophrenia (N:108)		Bipolar Disorder (N:100)	
		Mean ± SD		Mean ± SD	
Age		41.11 ± 10.24		41.45 ± 11.54	
		N	**%**	**N**	**%**
Sex	Female	27	25	60	60
	Male	81	75	40	40
Suicid Attempt	No	73	67.6	70	70
	Yes	35	32.4	30	30
Method of Suicide	Poisoning	22	62.8	17	56.6
	Jumping from a height	9	25.7	9	30
	Cutting or piercing	3	8.6	4	13.3
	Hanging	1	2.8	0	0
Type of Suicide	Violent	91	77.1	13	43.3
	Non-violent	27	22.9	17	56.6

(Abbreviations: SD, standard deviation).

Table 2
The Scale Scores of Patients.

Schizophrenia	**Mean ± SD**
PANSS pos.	11.61 ± 3.80
PANSS neg.	16.37 ± 5.25
PANSS psycho.	30.07 ± 7.31
PANSS total	58.09 ± 12.98
Bipolar Disorder	**Mean ± SD**
HAM-D	15.02 ± 9.18
YMRS	8.83 ± 10.39

(Abbreviations: SD, standard deviation; PANSS, positive and negative syndrome scale; HAM-D, hamilton depression rating scale; YMRS, young mania rating scale; pos., positive; neg., negative; psycho., psychopathology).

Table 3
Comparison of MBL2 Genotype Distribution of Attempted Suicide Patients Diagnosed with Schizophrenia to Non-attempted Schizophrenia Patients.

Schizophrenia	Attempted Suicide		p*
MBL2	no	yes	
AA	64(%87.7)	23(%65.7)	
AB	6(%8.2)	8(%22.9)	**0.026**
BB	3(%4.1)	4(%11.4)	
MBL2 (combined)			
AA	64 (%87.7)	23(%65.7)	**0.007**
AB/BB	9 (%12.3)	12(%34.3)	
MBL2 (allele)			
A	134 (%91.8)	54(%77.1)	**0.003**
B	12 (%8.2)	16(%22.9)	

* Pearson chi-square.

Table 4
Comparison of MBL2 Genotype Distribution of Attempted Suicide Patients Diagnosed with Schizophrenia to the Control Group.

Genotype			p*
MBL2	Control Group	Attempted Suicide	
AA	64(%64)	23(%65.7)	
AB	35(%35)	8(%22.9)	**0.012**
BB	1(%1)	4(%11.4)	
MBL2 (combined)			
AA	64 (%64)	23(%65.7)	0.855
AB/BB	36 (%36)	12(%34.3)	
MBL2 (allele)			
A	163 (%81.5)	54(%77.1)	0.430
B	37 (%18.5)	16(%22.9)	

* Pearson chi-square.

patients with BD were compared with the non-attempted BD patients, the MIF (GG, GC, CC) genotype (p = 0.038), (GG, GC/CC) combined genotype (p = 0.011) and the allele frequencies (G, C) (p = 0.006) distribution of attempted suicide patients with BD were found to be significantly different from the non-attempted BD patients. The percentage of the GC genotype and C allele was found to be statistically higher in the non-attempted BD patients compared to the BD with attempted suicide (Table 5). Again when the MIF (GG, GC, CC) genotype, combined genotype (GG, GC/CC) and the allele frequencies (G, C) of attempted suicide patients with BD were compared with the control group, the MIF (GG, GC, CC) genotype (p = 0.013), (GG, GC/CC) combined genotype (p = 0.003) and the allele frequencies (G, C) (p = 0.004) distribution of attempted suicide patients with BD was found to be significantly different from the control group. The percentage of the genotypes with mutation allele (GC/CC) and mutation allele (C) was found to be statistically higher in the control group compared to the BD with attempted suicide. (Table 6). When the MBL2 (AA, AB, BB) genotype, combined genotype (AA, AB/BB) and the allele frequencies (A, B) of attempted suicide patients with BD were compared with the non-attempted BD patients or the control group, there wasn't found to be significantly difference between the genotype distribution of the groups (p > 0.05) (Data not shown).

4. Discussion

Suicide is a major cause of death among patients with SCZ and the lifetime prevalence of suicide in patients with SCZ has been estimated to be ten times higher than among the general population [24]. Although no study was found in the literature that examined the relationship between MIF gene or MBL2 gene and SB in SCZ, Okazaki et al. reported that the MIF gene polymorphisms are associated with the risk for SCZ especially in adolescent females, and are potential stratification markers of SCZ [12]. Again, Foldager et al. found that the genotype ratio with the mutation allele was higher in this group compared to the healthy control group in the study about the association between MBL2 and SCZ [25]. In our study, while the distributions of the MBL2 genotype of attempted suicide patients in SCZ were statistically significantly different from the non-attempted SCZ patients, the distributions of MIF genotype of attempted suicide patients in SCZ weren't statistically significantly different from the non-attempted SCZ patients. In literature, genetic predisposition has been shown to contribute to the multifactorial risk model of SB in SCZ. Most of the studies have focused on genes involved in the serotonergic pathway. These studies have reported an association between variants in the serotonin transporter and TPH1 genes [24]. Hu et. al reported that

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Table 5
Comparison of MIF Genotype Distribution of Attempted Suicide Patients Diagnosed with the Bipolar Disorder to the Non-attempted Bipolar Disorder Patients.

Bipolar Disorder	Attempted Suicide		p*
MIF	no	yes	
GG	49(%70)	28(%93.3)	
GC	19(%27.1)	2(%6.7)	**0.038**
CC	2(%2.9)	0(%0)	
MIF (combined)			
GG	49 (%70)	28(%93.3)	**0.011**
GC/CC	21 (%30)	2(%6.7)	
MIF (allele)			
G	115 (%82.1)	58(%96.7)	**0.006**
C	25 (%17.9)	2(%3.3)	

* Pearson chi-square.

Table 6
Comparison of MIF Genotype Distribution of Attempted Suicide Patients Diagnosed with Bipolar Disorder to the Control Group.

Genotype			p*
MIF	Control Group	Attempted Suicide	
GG	66(%66)	28(%93.3)	
GC	31(%31)	2(%6.7)	**0.013**
CC	3(%3)	0(%0)	
MIF (combined)			
GG	66 (%66)	28(%93.3)	**0.003**
GC/CC	34 (%34)	2(%6.7)	
MIF (allele)			
G	163 (%81.5)	58(%96.7)	**0.004**
C	37 (%18.5)	2(%3.3)	

* Pearson chi-square.

tyrosine hydroxylase polymorphisms may contribute to the risk of attempted suicide in SCZ even after accounting for established clinical risk factors and ethnic stratification [26]. Another study about differences in expression of the dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32) gene, which is involved in dopamine, and possibly serotonin regulation, between patients diagnosed with SCZ who died by suicide and due to other causes. With regard to another frequently analyzed gene, the serotonin transporter 2A (HTR2A), there seems to be no firm evidence for an association [24].

It has been published that the MIF gene has a relationship with the HPA axis. The HPA axis has also been considered as a neurobiological factor related to suicide, nearly a 10-fold higher risk of completed suicide was found in dexamethasone suppression test (DST) non-suppressors than in DST suppressors in a depression [14,27]. In our study the MIF (GG, GC, CC) genotype, (GG, GC/CC) combined genotype and the allele frequencies (G, C) distribution of attempted suicide patients with BD was found to be significantly different from the non-attempted BD patients or control group. The percentage of MIF genotype (GC) of the BD patients without attempted suicide was found to be higher than the BD patients with attempted suicide. The percentage of MIF mutation allele (C) of the BD group without attempted suicide also was found to be statistically higher than the BD patients with attempted suicide. As a result of the literature review, only one study investigating the relationship between MIF and completed suicide was found. In contrast our study, Shimmyo et al. reported that the effects of MIF-794CATT$_{5-8}$ microsatellite and MIF-173G/C single-nucleotide polymorphism (SNP) on the MIF gene promoter might not contribute to the genetic risk of completed suicide in the Japanese population [14].

Although less is known concerning whether relationships of inflammatory pathways with suicide may be different from mood disorders. Only a few studies reported that such relationships exist. Increased levels of baseline inflammatory markers have been associated with depression and psychological stress which are well-determined risk factors for SB [28]. For instance, C-reactive protein (CRP) levels are higher among the attempted suicide patients diagnosed with mood disorder [29]. Again it was found that attempted suicide patients have increased serum levels of soluble IL-2 receptors compared to the control group [30]. Lindqvist et al. reported increased levels of IL-6 in the CSF of suicide attempters compared to the control group [31]. Janelidze et al. found that the levels of TNF-α and IL-6 were increased and the levels of IL-2 were decreased in patients who attempted suicide [32].

In our study, no significant difference was found between attempted suicide BD and non-attempted groups according to the variant of MBL2 which is involved in an innate immune response. In another study on the role of the innate immune system in attempted suicide, Pandey et al. reported that the protein expression of toll-like receptors-2 (TLR2), TLR3, TLR4, TLR6 and TLR10, and mRNA expression of TLR2 and TLR3 was significantly increased in the depressed suicide group compared with control group contrary to our study [33]. When other studies on SB in literature are reviewed, It was reported that violent SB in BD is associated with nitric oxide synthase 3 gene polymorphism [5]. Benedetti et al. also published a significant effect of Circadian Locomotor Output Cycles Kaput (CLOCK) gene variants and exposure to early stress on hopelessness and suicide in patients diagnosed with bipolar depression [34]. It was detected an association between suicide attempts and the inter-alpha-trypsin inhibitor heavy chain 3/4 (ITIH3/4) region in a combined group of patients with BD, SCZ and related psychosis spectrum disorders [35]. When the genetic association analyses examining polymorphisms within BDNF, COMT, cyclic AMP-responsive element-binding protein 1 (CREB1) and mitogen-activated protein kinase 1 (MAPK1) genes were performed in 259 bipolar patients according to suicide attempt, the significant associations were found with variations in rs13515 (MAPK1) and rs6740584 (CREB1) polymorphisms. No associations were found with polymorphisms within COMT and BDNF genes [6].

If the limitations of our study should be considered, MIF-173G/C single-nucleotide variants were examined, but it was not possible to know the other functional MIF-794CATT5–8 microsatellite variant of SCZ or BD with attempted suicide. Also, in our study, MBL2 gene polymorphism in codon 54 was examined, but it was not possible to know whether other polymorphisms which may disrupt MBL2 structure and prevent trimerization (mutations in codon 52 and codon 57) contributed to attempted suicide in SCZ or BD.

As a conclusion, we found that while the MBL2 gene variant may be associated with attempted suicide in patients diagnosed with SCZ, the MIF gene variant may be related to attempted suicide in BD patients. Confirmation of these findings with other gene variants in different ethnic populations may provide a better understanding of the relationship between MIF or MBL2 gene variants and attempted suicide in SCZ or BD.

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Statement of interest

All authors declare not to have any conflicts of interest that might be interpreted as influencing the content of the manuscript.

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Contributions of authors

HMA and SP are responsible for the formulation of overarching research goals and aims, integrity of the data and accuracy of data analyses. HMA, YO, MSY, AE, and SP conceived and designed the study. SP, YO and AE are the responsible provisions of study materials and laboratory samples. All authors acquired, analyzed, and interpreted all data. HMA drafted the manuscript. All authors critically revised the manuscript. SP and MSY supervised the study.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 [36].

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