

Metabolic Syndrome in First Manic Episode: A Comparison between Patients with or without Previous Depressive Episode

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Abstract

Objective: The purpose of this study was to investigate, whether an association between metabolic syndrome (MetS) and clinical features and affective temperaments exists or not in first manic episode of bipolar disorder (BD) with or without previous depressive episode.

Methods: Diagnosed with bipolar disorder type I according to DSM-IV criteria fifty four patients who were had a least one previous depressive episode (PDE) and 87 patients who were experiencing their first manic episode (FME) evaluated consecutively for inclusion. Comorbid axis I disorders and alcohol or substance use were excluded. NCEP ATP III formulated an operational definition of MetS based on the presence of three or more of the following characteristics: abdominal obesity (waist circumference), hypertriglyceridemia, low HDL or being on an antilipidemic agent, high blood pressure or being on an antihypertensive agent, and fasting hyperglycemia or being on antiglycemic agent. The patients who had been in remission period for at least 8 weeks were evaluated with SCIP-TURK and TEMPS-A. Remission was defined as YMRS score<5.

Results: MetS was found to be more frequent in these patients than the patients who didn't have a PDE. PDE, negative family history, childhood trauma and seasonality are determined as the predictors of MetS. Anxious temperament scores were higher in MetS (+) FME patients of both groups. Irritable temperament scores were higher only in MetS (+) FME patients without PDE group.

Conclusion: The presence of MetS seems to be correlated with the onset and progression of BD. This may also contribute to the discovery of biological markers, increase in our diagnostic tools, development of protective and individual-specific treatment options.

Keywords: Metabolic syndrome; First episode mania; Previous depressive episode

Introduction

Bipolar disorder (BD) is known to be associated with premature mortality [1]. Excess mortality rates due to medical disorders are between 1.5-3 times higher in adults with BD compared to general population. There is increasing evidence that indicates an inter-relationship between mood disorders and some physical diseases [2]. Glucocorticoid/insulin signalling mechanisms and inflammatory effector systems are intersections pointing to pathophysiological relationships between bipolar disorder and general medical conditions that are susceptible to stress as metabolic syndrome (MetS).

MetS is more prevalent in those with bipolar disorder than in the general population [3]. A subgroup of patients with bipolar disorder have a higher risk of developing MetS based on their habits, lifestyles, genetic susceptibility, and choices of treatment. A 35-40% prevalence of MetS has been reported in patients with bipolar disorder, and the MetS includes obesity, diabetes, hypertension, and dyslipidemia. Although they are not among the diagnostic criteria of MetS, the proinflammatory and prothrombotic states and purinerjic dysfunction are considered to be in the framework of metabolic syndrome [4,5].

Bipolar patients with a MetS have an adverse course and outcome, less favorable response to treatment, a greater risk for suicidality, higher rates of unemployment and thus higher cost [6]. On the other hand, having a medical condition was associated with longer duration of untreated illness and female gender [7]. In Perugi et al. study, length of pharmacological treatment and age at onset of first major episode were associated with the presence of comorbid MetS [8].

There aren't any studies that investigate MetS and their clinical and temperamental correlates in the first episode mania with drug

naive patients and at the onset of the illness. In the present study we aimed to investigate, whether an association between MetS and clinical features and affective temperaments exists or not in first manic episode of BD with or without previous depressive episode, and to clarify the prevalence and predictors of MetS in patients which were robustly defined.

Methods

Sample

A total of 200 patients who were admitted to the Erenköy Mental and Neurological Diseases Training and Research Hospital (Istanbul, Turkey) outpatient clinics or emergency services between 1 April 2011 and 1 April 2014 and received a diagnosis of bipolar disorder type I according to DSM-IV criteria and who were experiencing their first episode were screened consecutively for inclusion. Comorbid axis I disorders were excluded (n=41). Additional exclusion criteria were: (i) being outside the 18-45 age range (n=4), (ii) alcohol or substance use (n=6, and (iii) use of any psychotropic drugs within the last 24 hours for current manic episode (n=8).

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Received February 14, 2016; Accepted February 26, 2016; Published February 28, 2016

Citation: Kesebir S, Altıntaş M, Yaylacı ET, Erdiñç B, Tarhan N (2016) Metabolic Syndrome in First Manic Episode: A Comparison between Patients with or without Previous Depressive Episode. J Metabolic Syndr 5: 201. doi:10.4172/2167-0943.1000201

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Assesment tools

Structured Clinical Interview for DSM-Axis I Disorders-SCID-I Turkish version [9]. Mood Disorders Diagnosis and Following Form (SKIP-TURK) [10]. The SKIP-TURK was used to record age at disorder onset, duration of the disorder, age at treatment initiation, physical and sexual abuse in the history, family history, academic and social functioning, age at menarche, premenstrual syndrome, stressor prior to first episode, the type of first episode, severity of the episode (Global Assessment of Functionality –GAF- score), postpartum onset, seasonality, depression subtype, psychotic episode, suicide, hospitalization, duration of the episode, the number of the episodes, dominant course pattern, acute onset and remission, chronicity and rapid cycling, switch, cigarette smoking, and alcohol and other substance use.

Young Mania Rating Scale (YMRS) [11] was used to measure the severity of manic symptoms before treatment in manic cases and to confirm the state of remission in the recovery episode. We used the Turkish version, developed by Karadağ et al., which provides equivalent reliability to the original version [12].

Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) [13]. It was developed by Akiskal et al. to evaluate depressive, cyclothymic, hyperthymic, irritable and anxious temperaments. The reliability and validity study for the Turkish form was done by Vahip et al. [14].

Procedures

Ethical permission for the study was obtained from the Local Ethical Committee of Erenköy Mental and Neurological Disease Training and Research Hospital (Istanbul, Turkey). The cost for blood level measurements was met by our hospital's Investigation Budget Fund. An informed consent form was signed by a first-degree relative of patients experiencing a manic episode, than confirmed by the patient in remission period. Information for the SKIP-TURK was collected during the remission period with the patient and at least one first-degree relative. When a clear evaluation could not be performed, information about the illness was obtained from other relatives of the patient.

Blood samples necessary for the measurement were drawn from the brachial vein after at least eight hours of fasting within the first 24 hours. Use of a benzodiazepine was allowed for reasons of agitation. Simultaneous fasting blood glucose (FBG), C-reactive protein (CRP), uric acid and lipid levels (cholesterol, high and low density lipoprotein and triglyceride) were measured in the biochemistry laboratory of our hospital, using standard enzymatic procedures. Abdominal obesity was evaluated by measure of waist circumference.

The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) formulated an operational definition of MetS based on the presence of three or more of the following characteristics: abdominal obesity (waist circumference), hypertriglyceridemia, low HDL or being on an antilipidemic agent, high blood pressure or being on an antihypertensive agent, and fasting hyperglycemia or being on antidiabetic agent [15].

The patients who had been in remission period for at least 8 weeks were evaluated with TEMPS-A. Remission for the patients was defined as YMRS score <5.

Statistical analysis

The comparison of numerical variables was carried out using

t-tests, and Pearson's correlation test was used for correlation analysis. The comparison of categorical variables was carried out using chi-square test. Logistic regression was performed to obtain the predictive variables. Two-tailed tests were used on all findings and a p-value of <0.05 was considered statistically significant.

Results

Sample

75 female and 66 male first manic episode (FME) patients means of age was 28.3 ± 5.1 . 54 patients had a at least one previous depressive episode (PDE) and 44 of them had a psychopharmacological treatment for concurrent depressive episode (81.5%). MetS was found to be more frequent in these patients than the patients who didn't have a PDE (Table 1). Female gender was more frequent in FME with PDE group, while FME without PDE group was older.

The predictors of MetS in first manic episode

Presence of PDE, negative family history of BD, presence of childhood trauma and seasonality are determined as the predictors of MetS (OR=9.3, CI 95% 2.5-10.2, $p < 0.001$; OR=7.8, CI 95% 4.5-11.8, $p < 0.001$; OR=5.6, CI 95% 1.3-7.8, $p = 0.005$; OR=2.1, CI 95% 2.1-4.2, $p = 0.030$).

Comparing of MetS (+) and (-) patients

Mean of age of MetS (+) patients was lower in FME with PDE group while mean of age of MetS (+) patients was higher in FME without PDE group (Table 2).

Family history of BD was less frequent in MetS (+) FME patients with or without PDE while childhood trauma was more frequent (Table 2). Frequency of psychotic symptoms were similar between MetS (+) and (-) patients in two group. Premenstrual syndrome (PMS) was found to be more frequent only in MetS (+) patients who were FME with PDE.

Anxious temperament scores were higher in MetS (+) FME patients of both groups. Irritable temperament scores were higher only in MetS (+) FME patients without PDE group (Table 2).

Discussion

This is the first study that investigates MetS in patients with first manic episode which take into consideration of the presence of a previous depressive episode. MetS was found to be more frequent in FME with PDE group than FME without PDE. Moreover, presence of previous depressive episode was found to be the strongest predictor of MetS in regression analysis. Obviously, individuals with depression have an elevated risk of MetS [16]. At the same time according to our results, four-fifths of the patients with previous depressive episode, had used a psychopharmacological treatment for their mentioned depressive disorders. As a result it is worth to ask whether depressive episode itself or the psychopharmacological agents used to treat it was the cause of the higher MetS in these FEM patients with PDE.

According to Vancampfort et al. meta-analysis, antipsychotic use significantly explained higher MetS prevalence estimates in major

	FME with PDE n= 54	FME without PDE n= 87	Analysis p
MetS (%)	44.8	28.7	0.012
Age (mean \pm SD)	26.1 \pm 4.7	30.2 \pm 5.3	0.027
Gender (female/male)	19/8	42/45	< 0.001

Table 1: Sample.

	FME with PDE n= 54			FME without PDE n= 87		
	MetS (+) n= 24	MetS (-) n= 30	Analysis P	MetS (+) n= 25	MetS (-) n= 62	Analysis p
Age (mean ± SD)	23.7 ± 3.5	31.1 ± 4.2	0.005	34.5 ± 4.1	26.3 ± 2.9	0.001
Gender (female/male)	8/4	11/4	0.055	12/13	30/32	0.722
Family history (%)	16.6	66.6	<0.001	28	50	0.001
Childhood trauma (%)	41.6	26.6	0.018	64	35.5	0.015
YMRS (Mean ± SD)	27.5 ± 2.9	30.1 ± 3.2	0.422	34.3 ± 4.1	32.6 ± 2.7	0.375
Psychotic symptom (%)	25	33.3	0.279	32	33.9	0.831
Seasonality (%)	66.6	13.3	<0.001	-	-	-
PMS (%)	50	20	0.010	44	32.2	0.467
Depressive temperament (mean ± SD)	15.6 ± 2.5	14.7 ± 1.8	0.462	16.5 ± 2.3	17.7 ± 2.8	0.423
Cyclothymic temperament (mean ± SD)	13.4 ± 2.8	12.6 ± 1.5	0.567	14.3 ± 2.5	12.9 ± 1.7	0.267
Hyperthymic temperament (mean ± SD)	11.6 ± 3.4	12.1 ± 2.3	0.755	13.6 ± 3.4	15.1 ± 2.3	0.155
Irritable temperament (mean ± SD)	17.8 ± 2.3	16.3 ± 1.9	0.232	20.8 ± 2.1	17.3 ± 1.9	0.034
Anxious temperament (mean ± SD)	20.1 ± 2.3	17.5 ± 1.6	0.040	22.1 ± 2.6	18.2 ± 1.5	0.014

Table 2: Comparing of MetS (+) and (-) patients.

depressive disorder (MDD) [16]. Differences in MetS prevalences were not mediated by age, gender, geographical area, smoking, antidepressant use, presence of psychiatric co-morbidity. In another study, there was some mediating role for tricyclic and non-selective serotonin-reuptake inhibitor antidepressant use but overall, the mediating role of clinical differences were limited [17]. When Margary et al. evaluated 83 psychiatric inpatients diagnosed with schizophrenia, bipolar disorder and MDD they found a positive association between antidepressant drug treatment with triglycerides, and triglycerides/HDL ratio levels and antipsychotics drugs with the HOMA and Framingham index [18].

In Perugi et al.'s study, duration of pharmacological treatment and age at onset of first major episode were associated with the presence of comorbid MetS [8]. Specific features of MetS in psychiatric population are mainly represented by young age of onset, hyperinsulinemia, increased abdominal adiposity, and low HDL cholesterol whose common denominator may be insulin-resistance [18]. In our study, when tested between patients with or without MetS, mean of age of MetS (+) patients was lower in FME with PDE group while mean of age of MetS (+) patients was higher in FME without PDE group. In another words, onset of bipolar disorder is earlier in MetS (+) subjects of FEM with PED group. However, MetS (+) subjects of FEM without PED group is older. It means that, onset of bipolar disorder is relatively late in patients with MetS of this group. In accordance with this result, in one of our previous studies in which we investigated the incidence of diabetes in first episode mania patients, late onset was found as one of the predictors of diabetes development [19]. Also in one of our more recent studies in which we studied cellular adhesion molecules as a component of proinflammatory processes in first episode mania without previous depressive episode, the age of onset was found as 30.5

± 9.9 and this result could be considered as relatively old for the onset of bipolar disorder [4].

It is an important but yet unanswered question whether there is a relation of time or phase between bipolar disorder and MetS as both disorders has negative effects on the prognosis of one another and on selection and application of treatment modalities for both disorders. Soreca et al. suggested that comorbid medical conditions were independent of age but related to duration of bipolar disorder and they were related to some shared mechanisms and biological determinants [20]. In one of our prospective studies in which we evaluated 2000 consecutive patients who were admitted to our outpatient clinic and gave their informed consent, we investigated the process of diagnosis and treatment of MetS according to NCEP ATP III criteria in patients who were diagnosed as schizophrenia, bipolar disorder, recurrent major depressive disorder and anxiety disorder (generalized anxiety disorder, panic disorder, obsessive compulsive disorder) according to the DSM-IV [21]. In aforementioned study, assessments of 1816 patients were considered reliable and included in statistical analysis. When correlations of time elapsed since onset of Axis I psychiatric disorder and onset of MetS were tested, although these durations were found similar in affective disorders group (6.19 ± 7.55 and 7.12 ± 8.15) ($r=0.912$), value of r was 0.265 for anxiety disorders group (3.21 ± 3.15 and 8.34 ± 5.71) and 0.425 for schizophrenia group (13.82 ± 11.36 ve 8.21 ± 8.55) respectively. This results means that time of onset for affective disorders and medical conditions were relatively concurrent.

When comorbidity of medical conditions were evaluated in terms of phases of bipolar disorder, possibly they are more prevalent at onset and earlier episodes. This is because early mortality is observed more in patients with earlier onset [22]. Comorbid medical conditions that emerge in middle stages of bipolar disorder would possibly be related to the effect of treatment and effects of patient's habits and lifestyle. However it was showed that even in these circumstances they emerge one decade earlier than the age-matched subjects without bipolar disorder. When all these findings are taken together, it seems that MetS is one of the variables which is in a position as both an initiator and an outcome of bipolar disorder.

Negative family history of BD was related to MetS for the first time in this study. It was suggested as one of the predictive variables of MetS in patients with first episode mania. This result is very important as it suggests possible alternative etiological links apart from MetS and genetic factors for BD whose monozygotic concordance is 70%. Molecular genetic studies showed that, BD shares similar conversions and deletions in same loci with some general medical conditions including coronary artery disease, hypertension, diabetes mellitus type I and II [23]. However genetic association can only explain 10% of total variance of clinical co-existence [24]. This outcome, which researchers call "missing heritability", means that interactions with environmental influences have absolute role both in etiology and resilience in accordance with epigenetic principles. In this study childhood trauma is found as another predictive factor for MetS. This mentioned relationship was also suggested earlier by McIntry et al. [25]. Acute stress prompts a response by an inflammatory reaction in the brain [21]. Autonomic nervous system is directly activated. Release of adrenaline and noradrenaline is end up with their binding to alpha and beta adrenergic receptors on cytokine cells. Subsequently, nuclear factor kappa-beta mediated proinflammatory cytokine release starts. On the other hand, chronic stress leads to HPA axis disorders and consequent hypercortisolism, so childhood traumas are frequently associated with obesity, diabetes, coronary artery disease, chronic obstructive pulmonary disease and autoimmune diseases. At this

point abnormal stress response could play a role in the etiology of both a chronic psychiatric disorder and a comorbid medical condition. Hypertension and obesity are the medical conditions that are associated with childhood trauma in bipolar disorder [25]. Additionally, early menarche and EEG abnormalities are found as the projections of childhood trauma on bipolar disorder [25-27].

Although it's genetic aspects are set forth more clearly in recent years, seasonality is a variable which can also be evaluated in the context of epigenetic principles, and according to our results it is a predictor clinical factor for MetS in first episode manic patients. Environmental factors as seasonality affect susceptibility to allostatic load. It is amply documented that bipolar symptoms or episodes are affected by seasonality in susceptible subsets. It could be conceptualized that MetS is a phenotypic manifestation of an abnormal stress response with somatic manifestations [28]. It would be interesting to know whether individuals with MetS syndrome seasonality are more or less likely to also experience breakthrough symptomatology. The principal circadian clock generates seasonal variations in behavior as well. Seasonality elevates the risk for metabolic syndrome, and evidence suggests that disruption of the clockwork can lead to alterations in metabolism. Englund et al.'s findings support that relationship between circadian clocks and the MetS [29]. Circadian gene variants associate to the risk factors of MetS, that they were associated with hypertension and high fasting blood glucose.

Temperament originates in the brain structure, and individual differences are attributable to neural and physiological function differences. It has been suggested that temperament is associated with metabolic syndrome (MetS) markers, which may be partly mediated by lifestyle and socioeconomic status. Altunbaş et al. suggest that depressive temperament profiles may predispose an individual to the development of MetS in the winter [30]. In their study the proportions of MetS were 19.2, 23.1, 34.6, and 38.5% in the summer, fall, spring, and winter, respectively. Only depressive temperament scores were higher during the winter in patients with MetS.

Temperamental factors were related cross-sectionally to, as well as predicted for, the metabolic syndrome precursors over the 3-year period [31]. Mental vitality and positive emotionality were likely to be related and positive emotionality were likely to be related to a low MetS risk level, whereas hyperactivity, negative emotionality, responsivity to others, and cooperativeness were related to a high level of MetS risk. Same group's results showed that a temperament profile characterized by a high level of persistence and reward dependence, an average level of novelty seeking, and a low level of harm avoidance was related to a high level of MetS risk factors [32]. In a systematic review with thirteen cross-sectional analyses, and ten longitudinal analyses, hostility, anger, type A behavior and neuroticism and type D personality were associated with an increased prevalence of metabolic syndrome and its development over time [33]. In our study, two types of affective temperament were differentiated between MetS (+) and (-) subjects: Anxious and irritable temperaments. Hyperactivity, high level of persistence and reward dependence, average level of novelty seeking, and low level of harm avoidance which were reported in earlier studies are similar to the features defined for irritable temperament. Additionally, negative emotionality, responsivity to others and cooperativeness are features consistent with the properties defined for the anxious temperament. Anxious temperament overlaps with depressive temperament in terms of responsivity to others and cooperativeness. In this context, our findings are consistent with Altunbaş et al.'s results as well.

There are also studies that emphasizes the role of gender in the relationship between temperament and MetS. Rejave et al. stated that the relationship between MetS and hyperactivity and negative emotionality was more prominent in men. Sovio et al. assessed the association between temperament and metabolic syndrome in Northern Finland 1966 Birth Cohort [34]. According to their results novelty seeking was positively associated with waist circumference in both genders. However, systolic blood pressure was highest in men with high harm avoidance and low persistence scores, a profile consistent with anxious temperament and lowest in women with high reward dependence and high persistence scores, a profile consistent with irritable temperament. In one of our previous studies we detected an association between impulsivity and triglyceridemia specific for the anxious temperament [35]. When assessed separately for genders, the relationship between impulsivity and triglyceride levels was detected only in female bipolar patients [36]. In one of our following studies in which we investigated MetS components by gender in first episode subjects, we found triglyceride levels of female patients different from healthy controls [37]. In this study, gender difference between MetS(+) and (-) patients is close to statistical significance only in FME with PDE group and is more prominent in female gender. We know that anxious temperament is more common in females and irritable temperament is more common in males [14]. Anxious temperament differentiates in favor of MetS(+) in the FME with PDE group where female gender is predominant. In addition to this result, irritable temperament differentiates in favor of MetS as well in the FME without PDE group where gender distribution is similar between MetS(+) and (-) patients. We think that the reason for irritable temperament scores' undifferentiation in favor of MetS in FME with PDE group could be the presence of predominantly female gender distribution in this group. Female gender is a risk factor for MetS [7]. According to our results, the same applies to FME with PDE.

Affective temperament is a suggested endophenotype for BD as well. Cyclothymic ve hyperthymic temperaments are the ones that are found to be genetically associated with BD and different in patients and their healthy relatives from healthy controls [38]. In this study anxious and irritable temperaments which differentiate in MetS(+) patients, underlines the effect of environmental influences on the development of MetS once more. Irritable temperament was associated with mixed episodes in patients with BD [39]. According to McIntyre, obesity may affect the symptomatic presentation of BD, by increasing the likelihood that these patients will present with mixed episodes [28]. We think this is applicable not only to obesity but also to MetS. Inappropriate psychopharmacological antidepressant use may contribute to this situation directly by increasing the risk of mixed episode and indirectly by increasing the risk of MetS. On the other hand, there was no clear association between temperament measures and the occurrence and development of the metabolic syndrome. There is, however, a cluster of risk factors that include the presence of the metabolic syndrome, as well as a more negative prone temperament profile, that both predispose to the development of coronary heart disease and diabetes.

In conclusion, there is multidimensional explanation for bipolar disorders that is coherent, comprehensive, and explanatory. The presence of MetS seems to be correlated with the onset and progression of BD. It is possible that common risk factor are present in the onset of both metabolic syndrome and BD. This link could provide an interesting new paradigm for the study of the "systemic" nature of BD and the other mood disorders. This may also contribute to the discovery of biological markers, increase in our diagnostic tools, development of protective and individual-specific treatment options.

Acknowledgment

The authors have not any conflicts of interest and financial disclosures. Funding or support was not used for this investigation.

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