Metabolic syndrome in Italian patients with bipolar disorder: a 2-year follow-up study.

Metabolic syndrome in Italian patients with bipolar disorder: a 2-year follow-up study

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Abstract

Background: Metabolic syndrome (MetS) is highly prevalent in patients with bipolar disorder (BD). Few prospective studies have demonstrated an increase of MetS prevalence over time in patients with BD, but no study has tried to unveil the characteristics of patients with BD eventually developing the MetS. In our study we assessed the prevalence of MetS and its criteria over a period of 2-years; then, we identified the baseline clinical features of patients who developed the MetS during the follow-up with the intent to identify potential predictors for developing the MetS.

Methods: Subjects with BD consecutively admitted from April 2006 to September 2008 were included. MetS was diagnosed according to NCEP ATP-III modified criteria at baseline and after 2 years. We then selected patients without MetS at baseline and analyzed the association between clinical characteristics at baseline and the presence of MetS at follow-up by means of logistic regression analysis.

Results: 70 patients underwent all baseline and follow-up analyses. MetS prevalence significantly increased from 28.6 to 44.3% during the 2-years naturalistic follow-up ($p=0.027$). Significant predictors of MetS at follow-up were older age, higher BMI, and baseline exposure to antipsychotics.

Limitations: Lack of a healthy control group.

Conclusion: MetS can rapidly develop in patients with BD, especially if antipsychotics are prescribed. Our paper highlights the importance of regularly screening the MetS in patients with BD despite the presence of metabolic disturbances at baseline.

Introduction

Metabolic syndrome (MetS) is defined by a group of metabolic abnormalities such as central obesity, hyperglycemia, atherogenic dyslipidemia, and hypertension, which is associated with an increased prevalence of cardiovascular disease (Isomaa et al., 2001; Lakka et al., 2002), type II diabetes (Ford et al., 2002; Meigs et al., 2006) and stroke (Kurl et al., 2006).

Since obesity and diabetes have been found higher in patients with bipolar disorder (BD) than in the general population, there has been a rising concern about the issue of MetS in BD patients: several reports have indeed demonstrated that MetS is highly prevalent in patients with BD, with rates ranging from 36 to 49% in the USA (Cardenas et al., 2008; Fagiolini et al., 2008; Fiedorowicz et al., 2008) and from 18 to 26% in European countries (Birkenaes et al., 2007; Garcia-Portilla et al., 2008; van Winkel et al., 2008; Salvi et al., 2011). A recent review has found that patients with BD have a relative risk for MetS of 1.6 compared with the general population (Murray et al., 2009).

Together with illness-related factors such as the adoption of unhealthy lifestyles and probably inherited biological factors, psychopharmacological treatment plays an important detrimental role in inducing weight gain and metabolic abnormalities, eventually leading to the MetS. Indeed, several reports have highlighted a correlation between the use of medications such as atypical antipsychotics and mood stabilizers and weight gain, dyslipidemia and/or diabetes in patients with BD (Correl et al., 2006; Yumru et al., 2007). However, BD is a complex pathological entity, which often requires equally complex treatments involving the use of antipsychotics together with mood stabilizers (Zarate and Quiroz, 2003; Smith et al., 2007).

For this reason there is a need to identify which patients are at highest risk for developing MetS in the future, in order to avoid or give particular attention when employing combinations of mood stabilizers and atypical antipsychotics known for their metabolic side effects. These at-risk patients might also be involved in lifestyle modification programs aimed at avoiding the development of MetS.

Although the few follow-up studies performed to date have highlighted an increase in the prevalence of MetS over time (Guan et al., 2010; Taylor et al., 2010), no study has tried to unveil the characteristics of patients eventually developing the MetS. While older age and some ethnic groups have been consistently associated with the occurrence of MetS, clinical predictors of MetS are yet to be identified.

In this study we prospectively followed up patients with BD for two years, in order to evaluate the evolution of MetS and its components over a significant period of time. Then, we aimed at identifying the clinical features of the patients who gained the MetS status during the two-years follow-up. A broad range of factors was explored with the intent to identifying potential risk factors for MetS that should be examined further under controlled conditions.

Methods

The study had a prospective, naturalistic design, and involved patients consecutively admitted to the Psychiatric Inpatient Unit and to the Mood and Anxiety Disorders Outpatient Unit of the University of Turin (Italy), from April 2006 to September 2008. The majority of the sample has already been described in our previous cross-sectional study (Salvi et al., 2008).

Subjects

All patients with a diagnosis of BD type I, II, NOS, or cyclothymia (DSM-IV), were asked to participate. Potential participants were thoroughly explained study aims and procedures and had to give their written consent before participation.

Exclusion criteria were: age ≤ 18, pregnancy or postpartum, and refusal to consent participating in the study. All subjects were of Caucasian Italian origin.

Assessments and procedures

At study entry, general socio-demographic information was collected for each subject. The diagnoses of BD I, II were confirmed by the Structured Clinical Interview for DSM Axis I Disorders (SCID-I) (First et al., 1997). Clinical characteristics such as age at onset, duration of illness, number of previous manic/depressive episodes, history of suicide attempt, Axis I and II comorbidity were collected. Use of medications was also assessed: we specifically looked at the use of weight inducing medications such as mood stabilizers and antipsychotics.

Lifestyles were also investigated: information about exposure to cigarette smoking, use of alcoholic beverages, and physical exercise were obtained by directly interviewing the patients.

Comorbidity and family history for diabetes or cardiovascular diseases, and current treatments for hypertension, diabetes, or dyslipidemia were assessed by looking at medical reports, and by direct interview of the patients.

At baseline weight, height, waist circumference, and blood pressure were measured. Weight was measured undressed and fasting, height was measured barefoot. Patients with a Body Mass Index (BMI) ≥ 30 were categorized as obese according to the WHO classification (WHO, 1997; James, 2001). Waist circumference, measuring central adiposity, was taken at midway between the inferior margin of the ribs and the superior border of the iliac crest, at minimal respira-

tion. Two blood pressure measurements were obtained by using a mercury sphygmomanometer: the first with the subject in a lying position, the second with the subject in a seated position at least two minutes after the first measurement. The mean blood pressure of the two measurements was used. The attending physician in hospital setting performed all procedures.

A blood draw for routine blood exam was performed. Blood exams included glucose, total cholesterol, triglycerides, LDL and HDL-C. Blood samples were drawn in our clinic and examined in the "Baldi e Riberi" laboratory of analysis, San Giovanni Battista Hospital, Turin, Italy.

MetS was diagnosed according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III-modified criteria (Grundy et al., 2005):

- Abdominal obesity: waist circumference ≥ 102 cm in men and ≥ 88 cm in women
- Hypertriglyceridemia: ≥ 150 mg/dl or on lipid-lowering medication
- Low HDL-C: < 40 mg/dl in men and < 50 mg/dl in women
- High blood pressure: systolic pressure ≥ 130 mmHg and/or diastolic pressure ≥ 85 mmHg or on antihypertensive medication
- High fasting glucose: ≥ 100 mg/dl or on glucose-lowering medication

The measurements of the parameters for MetS diagnosis were repeated at baseline and after 2 years in order to identify changes in metabolic parameters and new onset MetS over time. Since we were interested in looking at the predictors of new onset MetS, we then excluded the patients with MetS or history of cardiovascular disease at baseline and looked at baseline demographic and clinical characteristics of the patients who developed the MetS during the 2-years follow-up.

Statistical analysis

Subjects characteristics were summarized as mean and SD for continuous variables and as percentage for categorical variables.

We calculated the prevalence of MetS and its criteria at baseline and follow-up in the whole sample. We assessed the change in waist circumference, blood pressure, triglycerides, HDL cholesterol, and glucose over time by way of paired-samples t-test, and assessed the change in the development of abdominal obesity, hypertension, hypertriglyceridemia, low HDL-c, hyperglycemia, and MetS at baseline and follow-up using McNemar's chi-square test for within-subjects variables. We then selected the patients who were free from MetS and cardiovascular disease/diabetes comorbidity at baseline and analyzed the association between socio-demographic and clinical characteristics at baseline and MetS at follow-up by means of independent-samples t-tests for continuous variables and chi-square test for categorical variables. Finally, we entered the baseline significant variables in a stepwise logistic regression analysis with MetS at follow-up as the dependent variable.

All data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL).

Results

One hundred-six patients were asked to participate. Eight patients had been excluded due to age below 18 years (4 patients), pregnancy (2 patients) and refusal of consent (2 patients). Ninety-eight patients were initially enrolled in the study. Twenty-eight patients underwent baseline assessment but were lost to follow-up; all of the following analyses were performed on the 70 patients who were assessed at baseline and after 2 years of follow-up.

The mean age of the patients was 51.2 years, 64% were females. The majority of the sample (68.6%) had bipolar II disorder; the mean duration of illness was 20.6 years. Patients were on a mean of 2.6 medications for bipolar disorder; 90% were receiving at least one mood stabilizer, 40% were receiving at least one antipsychotic, and 55.7% were treated with at least an antidepressant. The mean BMI was 26.4 kg/m^2. All baseline socio-demographic and clinical characteristics of the sample are shown in Table 1.

MetS prevalence significantly increased from 28.6 to 44.3% during the 2-years naturalistic follow-up (Table 2). Waist circumference significantly increased from 94.2 to 98.9 cm (t=-3.432, df=68; p=0.001) and glucose significantly increased from 81.6 to 95.6 mg/dl (t=-4.867, df=69; p<0.001), while blood pressure, triglycerides, and HDL levels did not change over time. Hyperglycemia was the only criteria that changed significantly over the 2 years, from 14.3% at baseline to 31.4% at follow-up (χ^2=1.277, df=1; p=0.004)(Table 2).

At baseline, 20 of the 70 participants (28.6%) fulfilled the MetS definition and were excluded from the incidence analysis.

Of 50 patients without the MetS at baseline, 16 (32%) gained the MetS status during the follow-up. At baseline these patients were older (57.7 vs. 43 years; t=-4.009, df=48, p<0.001), had a higher age at onset (34.8 vs. 26.3 years; t=-2.431, df=48, p=0.019), a higher BMI (27.3 vs. 24.1; t=-2.561, df=48, p=0.014), had a higher family history for diabetes/cardiovascular disease (87.5% vs. 58.8%; χ^2=4.112, df=1, p=0.043), and were more frequently taking antipsychotics than patients not developing MetS over the follow-up (68.8% vs. 26.5%; χ^2=8.104, df=1, p=0.004). Patients who developed the MetS also showed a trend for higher rates of hypertension (50% vs. 23.5%; χ^2=3.503, df=1, p=0.061) and for taking

more psychotropic medications (2.9 vs. 2.4; t=-1.933, df=48, p=0.059) at baseline. Lifestyles did not predict MetS at follow-up.

All clinical characteristics of the patients developing and not developing the MetS are shown in Table 3.

When we entered age, age at onset, BMI, family history for diabetes/cardiovascular disease and baseline exposure to atypical antipsychotics in the logistic regression model, with MetS as the dependent variable, age at onset and family history for diabetes/cardiovascular disease were no more statistically significant, while age (B=0.143, S.E.=0.047, p=0.002), BMI (B=0.307, S.E.=0.116, p=0.008), and exposure to AP (B=-2.365, S.E.=0.962, p=0.014) significantly predicted the MetS at follow-up.

Discussion

This study found that metabolic syndrome rapidly increases over time in a sample of patients with bipolar disorder treated as usual. In our sample, the prevalence of MetS increased from 28.6 to 44.3% over the 2 years follow-up. Few follow-up studies have prospectively assessed the prevalence of MetS in patients with BD. A US study conducted on a mixed sample of 24 patients with BD and 30 with MDD found an increase of MetS prevalence from 11 to 17% over the two-years follow-up (Taylor et al., 2010). The 6% increase is of outstanding relevance since the patients were young and drug-naïve. A naturalistic Chinese study found a remarkable increase in MetS prevalence from 11 to 21% in only 6 months. Patients developing the MetS during the 6-months follow-up were more often alcohol drinkers and had more often hypertension at study endpoint (Guan et al., 2010).

In our study, we noticed that almost 30% of the patients that were healthy at baseline developed the MetS over a span of 2 years. This high incidence of MetS is partly unexpected, since patients were not drug-naïve at entry in the study and the increase in age at the end of follow-up was probably too small to determine such an effect. However, this phenomenon may have other explanations: in the incidence analysis we only excluded patients with MetS, leaving in the study many patients who already fulfilled one or two criteria for MetS at baseline; some of them developed a third metabolic abnormality during follow-up, being therefore classified as having the MetS. Furthermore, patients who agree to be evaluated at both baseline and follow-up are those who continue to come to medical visits and are most likely compliant with the medications prescribed. As further discussed, the majority of these apparently healthy patients had been prescribed atypical antipsychotics and might have continued in taking these medications despite upcoming weight gain, eventually developing other metabolic abnormalities.

Many parameters, such as blood pressure and lipids levels, do not change over time. On the contrary, abdominal fat and glycemic levels markedly grow over time, and seem to drive this increased prevalence of MetS. Indeed, visceral fat deposition and insulin resistance are considered early factors in the pathogenesis of MetS, eventually leading to dyslipidemia and hypertension (Eckel et al., 2005). Since even young, drug-naïve patients with BD are more frequently overweight (Maina et al., 2008), this can be especially true in patients with BD.

Since no study to date has identified the clinical predictors of MetS, we looked at the baseline clinical characteristics of the patients who did not have the MetS at

entry in the study and eventually developed it after two years. As expected, these patients were around 15 years older than those not developing the MetS, confirming age as one of the main risk factors for metabolic disturbances. Age has been invariably linked with MetS in studies performed on both general population samples (Ford et al., 2004; Hu et al., 2004) and patients with BD (Cardenas et al., 2008; Salvi et al., 2008; Sicras et al., 2008; van Winkel et al., 2008; Guan et al., 2010; Salvi et al., 2011).

Aging is commonly accompanied by a loss of muscle mass and by an increase in body fat, particularly in the abdomen; both of these changes can increase insulin resistance and eventually lead to MetS (Alberti et al., 2006).
Surprisingly, we also found that patients who developed the MetS over time had a later onset of the bipolar illness. A possible explanation of this finding is a recall bias due to the older age of the patients who developed MetS: elderly patients with a long history of illness may place the onset of their illness not so backward in time, thus shifting the age at onset later in time, and the information on age at onset mostly relied on the patients themselves, making this bias possible. However, when age at onset was entered in the logistic regression analysis it was no longer significantly associated with the development of MetS at follow-up.

More interestingly, patients developing the MetS over time were taking antipsychotics at baseline, most of which were atypical antipsychotics, confirming the increased risk associated with this class of medications. This is a relevant finding, since although many atypical antipsychotics are known for their dysmetabolic and weight-inducing activity none of the published cross-sectional studies has highlighted such an association, probably because of a 'confounding by indica-

tion' bias: patients already displaying the MetS features may have been prescribed medications less likely to induce weight gain and metabolic abnormalities. On the contrary, apparently healthy patients are more likely to be prescribed atypical antipsychotics that, on the long run, lead to the occurrence of MetS and can consequently lead to adverse cardiovascular outcomes. A limitation in our study is the lack of a more accurate evaluation of antipsychotic exposure during the follow-up: for example, patients taking antipsychotics at baseline may have stopped the antipsychotic after some months, thus biasing the results. However we found that the exposure to antipsychotics at endpoint was only slightly higher in patients without the MetS at baseline, thus suggesting that the patients continued taking almost the same treatments during the follow-up period.

Lifestyles did not predict MetS outcome at follow-up. In an important recent study, 275 obese patients with severe mental illness undergoing a structured physical exercise program for 12 weeks experienced a weight and glucose levels reduction; the prevalence of MetS was also reduced at endpoint (Lindenmayer et al., 2009). Although in our study we could not find a protective effect of performing physical exercise, our patients were not enrolled in specific exercise programs, thus physical exercise in our patients was probably too mild and unstructured to carry significant benefits.

In conclusion, MetS is a condition that often affects patients with BD. Our study further demonstrates that apparently healthy patients in their 50-60 years of age can rapidly develop the MetS, especially if atypical antipsychotics are prescribed,

and should therefore be regularly screened for MetS even though they do not display significant metabolic abnormalities at index visit.

A position statement from the European Psychiatric Association, the European Association for the Study of Diabetes and the European Society of Cardiology recommend the annual screening of cardiovascular risk factors in patients with severe mental illness (De Hert et al., 2009). Our study support the recommendation of regularly screening the MetS in patients with BD on psychopharmacological treatment, especially in those with older age and regardless of the presence of recognizable cardiovascular risk factors at index visits.

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Table 1. Socio-demographic and clinical characteristics of the sample at baseline (n=70).

Females, n (%)	45 (64.3)
Age (years), mean ± *sd*	51.2 ± 14.4
Education (years), mean ± *sd*	12.0 ± 4.1
BD type I, n (%)	22 (31.4)
Age at onset (years), mean ± *sd*	30.6 ± 12.4
Duration of illness (years), mean ± *sd*	20.6 ± 12.2
At least one suicide attempt, n (%)	24 (34.3)
Number of drugs for BD, mean ± *sd*	2.6 ± 0.9
Mood stabilizers, n (%)	63 (90.0)
Antipsychotics, n (%)	28 (40.0)
Antidepressants, n (%)	39 (55.7)
BMI, mean ± *sd*	26.4 ± 4.8

BD: Bipolar Disorder; BMI: Body Mass Index

Table 2. Components of metabolic syndrome at baseline and follow-up (n=70).

	Baseline	**Follow-up**	***p-value****
Abdominal obesity, n (%)	37 (52.9)	45 (64.3)	0.096
Hypertriglyceridemia, n (%)	21 (30.0)	21 (30.4)	1.000
Low HDL-c, n (%)	17 (25.4)	25 (35.7)	0.189
Hypertension, n (%)	34 (48.6)	37 (52.9)	0.664
Hyperglycemia, n (%)	10 (14.3)	22 (31.4)	0.004
MetS, n (%)	20 (28.6)	31 (44.3)	0.027

* using McNemar non-parametric test

Table 3. Baseline characteristics of healthy patients and MetS at follow-up (n=50).

	MetS (n = 16)	**No MetS** (n = 34)	**t/c2**	***df***	***P***
Age (years), mean ± *sd*	**57.7 ± 12.4**	**43.0 ± 12.0**	**-4.009**	**48**	**<0.001**
Education (years), mean ± *sd*	13.3 ± 4.8	11.6 ± 3.3	-1.519	49	0.135
Bipolar disorder, type I, n (%)	6 (37.5)	11 (32.4)	0.128	1	0.720
Age of onset (years), mean ± *sd*	**34.8 ± 9.6**	**26.3 ± 12.4**	**-2.431**	**48**	**0.019**
Duration of illness (years), mean ± *sd*	22.9 ± 13.1	16.8 ± 9.7	-1.836	48	0.073
N. of manic episodes, mean ± *sd*	4.2 ± 7.2	3.0 ± 2.0	-0.631	16.09	0.537
N. of depressive episodes, mean ± *sd*	6.7 ± 7.2	4.2 ± 2.8	-1.346	17.11	0.196
At least one lifetime suicide attempt, n (%)	3 (18.8)	13 (38.2)	1.898	1	0.168
Axis I lifetime comorbidity, n (%)	5 (31.3)	15 (44.1)	0.751	1	0.386
Axis II comorbidity, n (%)	2 (12.5)	7 (20.6)	0.482	1	0.487
CV family history, n (%)	**14 (87.5)**	**20 (58.8)**	**4.112**	**1**	**0.043**
Tobacco smoke, n (%)	8 (50)	17 (50)	<0.001	1	1.000
Alcohol consumption, n (%)	5 (31.3)	5 (14.7)	1.861	1	0.172
Physical activity, n (%)	7 (43.8)	19 (55.9)	0.642	1	0.423
N. of medications for BD, mean ± *sd*	2.9 ± 0.8	2.4 ± 0.8	-1.933	48	0.059
Mood stabilizers, n (%)	16 (93.8)	29 (85.3)	0.737	1	0.391
Antipsychotics, n (%)	**11 (68.8)**	**9 (26.5)**	**8.104**	**1**	**0.004**
Antidepressants, n (%)	8 (50)	20 (58.8)	0.344	1	0.558

BMI, mean ± *sd*	**27.3 ± 3.8**	**24.1 ± 4.2**	**-2.561**	**48**	**0.014**
Abdominal obesity, n (%)	7 (43.8)	15 (44.1)	0.001	1	0.981
Hypertriglyceridemia, n (%)	2 (12.5)	3 (8.8)	0.163	1	0.686
Low HDL-c, n (%)	3 (20)	5 (15.6)	0.138	1	0.710
Hypertension, n (%)	8 (50)	8 (23.5)	3.503	1	0.061
Hyperglycemia, n (%)	0 (0)	1 (2.9)	0.480	1	0.488