Psychiatria Danubina, 2014; Vol. 26, No. 3, pp 200-204 *Original paper*

LIFETIME HYPOMANIC SYMPTOMS IN REMITTED PATIENTS WITH SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

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received: 23.12. 2013; revised: 5.6.2014; accepted: 2.7.2014

SUMMARY

Background: *Clinical, genetic and neuroimaging studies indicated strong evidence against traditional diagnostic separation of bipolar disorder from schizophrenia. In this study, we aimed to evaluate hypomanic symptoms and influence on general functioning among psychotic patients.*

Subjects and methods: *Patients with schizophrenia and other psychotic disorders were assessed between June and September 2010. Positive and Negative Symptom Scale (PANSS), Hypomania Check List-32 (HCL-32), Mood Disorders Questionnaire (MDQ) and General Assessment of Functioning Scale (GAS) were applied to all 93 patients. Answers of self-rating scales were confirmed with hospital records.*

Results: *Mean age was 35.7±9.5 years, mean age of onset was 20.3±5.3 years and duration of illness was 15.4±9.2 years. 30.1% of the patients, had a history of mood stabilizer treatment taken at least one month while one five of the patients had different psychiatric diagnosis other than current diagnosis. 26.9% of the patients with psychotic disorders had positive scores on both MDQ and HCL-32 but there were no significant difference between patients in terms of general functioning (p=0.82).*

Conclusions: *As reported in this study, there is no simple, clear-cut between schizophrenia and bipolar affective disorder.*

Key words: *schizophrenia - hypomanic symptoms – dimensions - classification*

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INTRODUCTION

Emil Kraepelin's suggestion at the turn of the 20th century that manic depression could be differentiated from dementia praecox strongly influenced western psychiatry within a relatively short period (Altınbaş et al. 2011). Although Kraepelin's fundamental dichotomy has persisted for many years, vigorous debates about nosology have often occurred (Altınbaş et al. 2011, Angst & Gamma 2008, Crow 2008, Fischer & Carpenter 2009). Eugen Bleuler (1924) disagreed with Kraepelin, conceptualizing the relationship between affective illness and schizophrenia as a continuum without a sharp line of demarcation. According to Bleuler's view, a patient was either predominantly schizophrenic or predominantly manic-depressive with most patients situated somewhere along this spectrum (Goodwin & Jamison 2007). Eventually, the view that bipolar disorder and schizophrenia are mainly distinct diagnostic entities has been widely accepted in recent decades as reflected in the current classifications systems, the American Psychiatric Association's Diagnostic and Statistical Manual, fifth revision (DSM-5) and the World Health Organization's International Classification of Diseases, tenth edition (ICD-10). This is despite the reality that many individuals with severe psychiatric illness have both prominent mood and psychotic symptoms – raising the possibility, and indeed the likelihood, that there is no simple, clear-cut biological (and diagnostic) distinction between schizophrenia and bipolar disorder.

Family studies, twin studies, genome-wide linkage studies and association studies fail to support the traditional diagnostic separation of bipolar disorder from schizophrenia (Craddock et al. 2005). Whereas it was originally thought that schizophrenia was an illness of delusions and hallucinations, Crow was the first to suggest the existence of more than one "syndrome" of schizophrenia, that may involve more than one disease process (Crow 1980). Recent studies using complex statistical methods indicate that schizophrenia includes different syndromes, including positive symptoms, negative symptoms, disorganization, mania and depression (Dikeos et al. 2006, Boks et al. 2007, Egli et al. 2009). It is now well established that mood symptoms (both depressive and manic) are relatively common in patients with schizophrenia. Furthermore, depressive symptoms have been shown to have significant prognostic implications for patients with schizophrenia, with depressive symptoms in the acute psychotic phase of the illness an indicator of better prognosis, but post-psychotic depression an

indicator of poorer prognosis (Oosthuizen et al. 2008). Based on such findings, we aim to evaluate (hypo)manic symptoms in schizophrenia and other psychotic disorders and their impact on functioning.

SUBJECTS AND METHODS

Participants and study protocol

Schizophrenic and other psychotic patients attending to outpatient clinics were assessed for recruitment process according to inclusion and exclusion criteria. Patients between the ages 18-65 years and diagnosed with Schizophrenia or other psychotic disorders (delusional disorder, schizoaffective disorder, Psychosis Not Otherwise Specified (NOS)) were recruited for the study. Exclusion criteria were diagnosis of brief psychosis, schizophreniform disorder, history of alcohol and drug use disorder, Positive and Negative Symptom Scale (PANNS) scores >50 and hospitalization in the last 2 months. All patients signed written informed consents for participating to the study and local ethic committee approval was taken.

Data collection

Patients were assessed consecutively between 1st June-1st September. Ninety three patients were included for the study according to inclusion and exclusion criteria as defined above. The PANSS, Hypomania Check List-32 (HCL-32), Mood Disorders Questionnaire (MDQ) and General Assessment of Functioning Scale (GAS) were applied to all patients by two experienced clinicians (S.Y. and H.I.A.) and clinical diagnoses were confirmed with Structured Clinical Interview for DSM Disorders-I.

MDQ and HCL-32 both are self-report instruments which screen lifetime history of manic and/or hypomanic symptoms. MDQ includes 13 yes/no questions mainly derived from DSM-IV in the first sub-item and second sub-item asks whether several of any reported manic or hypomanic symptoms or behaviors were experienced during the same period of time. Lastly, the level of functional impairment related with these manic and/or hypomanic symptoms are asked with a 4-point scale (Hirschfeld et al. 2000).Other mood questionnaire, HCL-32 assesses symptoms in greater detail than DSM IV based structured clinical interview with 32 questions screening manic and/or hypomanic symptoms including active-elevated and irritable-risk taking sub-scales (Angst et al. 2005). The optimal cut-off points have been reported to be a score of 7 or higher for MDQ and 14 or higher for HCL-32.GAS is a rating scale developed for evaluating the overall functioning of an individual for a specified time period on a continuum from severe psychiatric symptoms to health (Endicott et al. 1976).

Socio-demographic and clinical variables of patients were completed during interviews with the patients and confirmed using hospital records. “Positive scores” that shows high probability of a mood disorder considered as higher scores on the cut of point (≥14) of the HCL-32 and MDQ (≥7 positive answers on the first item and yes answer for the second item).

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) 13 for Windows. Descriptive statistics were used for defining socio-demographic and basic clinical variables (e.g. illness onset, duration of illness). The chi-square test was used to compare the nominal and ordinal demographic variables. The Mann-Whitney U test was used for comparing GAS scores of the patients with and without positive mood scores on the MDQ and HCL-32 scales. Differences were considered significant at $p<0.05$ for all tests.

RESULTS

Most of the patients were male (n=70, 75.3%), not married (n=78, 83.9%) and only 21.5% of patients (n=20) were currently in employment. Diagnosis of the patients were schizophrenia (n=80, 86%), psychosis NOS (n=11, 11.8%), schizoaffective disorder (n=1, 1.1%) and delusional disorder (n=1, 1.1%). The mean age of patients was 35.7±9.5 years, mean age of onset was 20.3±5.3 years and duration of illness was 15.4±9.2 years. Approximately one third of the patients (n=28, 30.1%) had a history of mood stabilizer treatment taken for at least one month (Valproate n=20, Carbamazepine n=4, Lithium n=3, Lithium + Valproate n=1). Family history of psychiatric disorders among first degree relatives of patients was 37.7% (Psychotic disorders: 16.1%, depression: 15.1%, hospitalized but diagnosis could not be clarified: 3.2%, taking treatment but diagnosis could not be clarified: 2.2%, anxiety disorder: 1.1%).

The proportion of patients who scored ≥7 to the first item and answered yes to the second item of the MDQ was 29.0% (n=27). Also, 36.6% (n=34) of patients experienced ≥14 hypomanic symptoms on the HCL-32. The proportion of the patients who had positive scores on both the MDQ (7 or higher scores on the first item and yes answer for the second item) and HCL-32 (14 or higher scores) were 26.9% (n=25) that shows high probability of a mood disorder.

The mean scores of MDQ, HCL-32, PANSS and GAS are summarized in Table 1. There was no statistically significant difference between patients with and without positive mood scores in terms of age (p=0.66), duration of illness (p=0.72), total PANSS (p=0.96) and GAS scores (p=0.82) (Table 2).

Table 1. Descriptive values of the Symptom Scales

Scale	Min.	Max.	Mean	Median	SD
PANSS-P	7.0	9.0	8.7	8.0	2.4
PANSS-N	7.0	42.0	10.7	8.0	5.3
PANSS-G	16.0	40.0	18.7	16.0	4.5
MDQ(item 1)	0	14.0	4.1	3.0	4.3
HCL-32(item 3)	0	28.0	8.1	13.0	9.8
GAS	30	90	48.2	40.0	13.7

HCL-32: Hypomania Checklist-32, MDQ: Mood Disorders Questionnaire, PANSS: Positive and Negative Symptom Scale
GAS: General Assessment of Functioning Scale

Table 2. Comparison of General Functioning

Positive mood scores	Mean GAS score	Z	p*
Yes	45.5	-0.23	0.82
No	46.9	-0.23	0.82

*Compared with Man-Whitney-U test, p>0.05 non-significant

DISCUSSION

In recent years, emerging evidence from clinical, neuroimaging and genetic studies suggests that the division between both unipolar depression and bipolar disorder and between bipolar disorder and schizophrenia is likely to be over-lapping (Craddock et al. 2005, Crow 1980, Dikeos et al. 2006, Boks et al. 2007, Egli et al. 2009, Lichtenstein et al. 2009, Craddock & Sklar 2013). A dimensional classification of mood and psychotic disorders has been proposed by several authors in the light of the evidence that genetic factors for schizophrenia and the mood disorders overlap (Craddock et al. 2004, Angst 2007, Malhi et al. 2008, Abrams et al. 2008, Henry & Etain 2010, Juli et al. 2012, Potuzak et al. 2012.). The DISC1 (Disrupted in Schizophrenia 1) and NG1 (Neuregulin-1) genes can be considered good examples of overlap as these genes are found to be associated with mixed features of schizophrenia and mania, or unitary psychosis (Green et al. 2005, Hodgkinson et al. 2004). In line with the genetic evidence, neuroimaging studies indicate that bipolar disorders and schizophrenia share similar brain regions such as the prefrontal cortex, thalamus, left caudate, left medial temporal lobe, and right insula (Yu et al. 2010).

On the other hand, clinical data analyses with advanced statistical methods such as cluster analyses and factor analyses suggest that schizophrenia consists of many different syndromes. These syndrome clusters are mainly include positive symptoms, negative symptoms, mania, depression and disorganizations. These syndromes are not unique to schizophrenia only as existed in mood disorders (Ratakonda et al. 1998, Murray et al. 2005, Allardyce et al. 2007, Lage et al. 2011). In line with these findings, we found that 26.9% of the patients with schizophrenia or psychotic disorder have had both prominent mood and psychotic symptoms which supports the dimensional model. Consistently, one fifth of the patients had different psychiatric diagnoses other than their current diagnosis during their illness course and 15.1% of their first degree relatives had history of depression that may indicate genetic heterogeneity of psychotic disorders. Moreover, Boks et al. (2007) reported different clusters of symptoms in patients with schizophrenia, including depressive and manic symptoms providing an evidence for spectrum model. Furthermore, Häfner and colleagues (2008) evaluated the data of 107 patients with schizophrenia and found that 18% of the patients experienced nonpsychotic depressive episodes over a mean follow-up of 134 months (11.2 years). They also reported that patients with schizophrenia experienced manic symptoms for up to 5.8 months and that the prevalence of manic symptoms per month was up to 40% (over 134 months of follow-up). Overall, depression remained the most frequent syndrome during the course of schizophrenia. Similarly, Bressan et al. (2003) conducted a one-year follow-up study of first episode schizophrenia and found that 16.3% of the psychotic episodes fulfilled the DSM-IV criteria for a major depressive episode. Although the prevalence of depressive symptoms and episodes studied varied widely, data on the hypomanic/manic symptoms in schizophrenia is still limited. The reason might be related with the diagnosis of schizoaffective disorder which may reflect the co-occurrence of mood and psychotic disorders.

Recently, there is still a debate on the diagnostic stability and reliability of schizoaffective disorder even it remains in DSM-5 (APA 2013). The relative lack of stability and reliability of diagnoses influences other aspects of schizoaffective disorder, including functioning.Although there are studies suggesting that the long-term functioning of persons with schizoaffective disorder is similar to schizophrenia (Dissanayake et al. 2011, Kotov et al. 2013), there is a consensus that patients with schizoaffective disorder have better functioning than patients with schizophrenia but worse than those with mood disorders (Ratakonda et al. 1998, Bressan et al. 2003, Hodgkinson et al. 2004, Green et al. 2005, Murray et al. 2005, Allardyce et al. 2007, Angst

2007, Abrams et al. 2008, Hafner et al. 2008, Henry & Etain 2010, Yu et al. 2010, Lage et al. 2011, Kantrowitz & Citrome 2011). From here, it could be concluded that existence of mood symptoms might be related with better functioning in psychotic disorders even we could not find any difference between psychotic patients with and without positive mood scores.However, GAS is mainly a rating scale for evaluating the overall functioning and this may cause a type 2 error.

Our study has several limitations. First, we used self-rating scales for evaluating hypomanic/manic symptoms, even though patients were clinically remitted. Exclusion of relatively severe psychotic patients might cause a selection bias considering the negative correlation between affective and psychotic symptoms. Second, GAS is not a sensitive scale for detecting the influence of mood symptoms on functioning - it is widely used in clinical practice but not commonly used in research studies. Third, it would be preferable to conduct a prospective study for detecting the relationship between lifetime hypomanic symptoms and current functioning, instead of a cross-sectional design as we did. Fourth, our sample was relatively small and heterogenous. Lastly, we did not take into account the third item (functionality) of MDQ which may produce higher percentage of positive mood scores than they it was even it was confirmed with HCL-32.

Despite these limitations, our results are important for indicating evidence for the validity of a dimensional classification of psychiatric disorders. To the best of our knowledge, this may be the first study which specifically assesses the influence of life-time hypomanic/manic symptoms on general functioning among psychotic patients.

CONCLUSIONS

The DSM and ICD classifications have been very helpful for research and clinical practice but it may be appropriate to consider a return to a broader view of psychiatric disorders. The distinction between schizophrenia and bipolar disorder may not be as clear as the current classification system implies. Thus we suggest that a spectrum or continuum concept may provide a useful way to integrate a variety of observations concerning both mood and psychotic disorders. However, we did not find any difference in terms of functioning measured by GAS, it can also be concluded that our findings data do not provide evidence that dimensions would be helpful clinically. Besides, prospective studies evaluating different aspects of functioning specifically would lead a better model for dimensional view. Dimensional approaches may also allow clinicians to more fully characterize individual patients with a long-term view to developing much more rational psychological and pharmacological interventions.

Acknowledgements: None.

Conflict of interest: None to declare.

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