Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Neurological soft signs in euthymic bipolar I patients: A comparative study with healthy siblings and controls

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ARTICLE INFO

Article history:
Received 17 January 2015
Received in revised form
28 July 2015
Accepted 27 November 2015

Keywords:
Neurological soft signs
Bipolar I disorder
Case control study
Healthy siblings
Neurodevelopmental hypothesis

ABSTRACT

Neurological Soft Signs (NSS) are endophenotypic markers widely studied in schizophrenia and remain poorly evaluated in bipolar disorder. The aims of this paper were to determine the prevalence and scores of NSS in bipolar I patients, compared to healthy siblings and controls and to explore correlations with socio-demographic and clinical features of patients. This was a case-control study comparing 92 euthymic bipolar I patients, 44 of their healthy siblings and 60 control subjects. The neurological assessment was performed through the NSS scale validated by Krebs et al. (2000). Bipolar I patients were also assessed with the Bech-Rafaelsen Mania Scale (MAS), the Hamilton Depression Rating Scale (HDRS) and the Global Assessment of Functioning (GAF). The raters were not blinded to groups. The prevalence and the total score of NSS were significantly higher in bipolar I patients compared to their healthy siblings and controls. The sibling group had significantly higher NSS prevalence and total score than controls. No correlation was found between NSS total score and socio-demographic and clinical features of patients, except a negative correlation with the school level and the GAF score. In conclusion, bipolar I patients have motor and sensory signs, which are unrelated to their clinical features.

1. Introduction

Bipolar disorder (BD) is a recurrent disease, with severe mood relapses and a difficult management. Its medical and economic implications are serious (Hakkaart-van Roijen et al., 2004; Young et al., 2011) and it is associated with significant impairment in work, family and social life (Sanchez-Moreno et al., 2009).

The etiopathogenesis of BD is complex, involving genetic (Seifuddin et al., 2012), biological (Maletic and Raison, 2014) and psychosocial (Alloy et al., 2005) factors. Thus, various hypotheses to explain this disorder were advanced including the neurodevelopmental one which was first proposed by Weinberger in schizophrenia (Weinberger, 1987). This hypothesis stipulates the interaction between genetic and environmental factors at crucial moments of brain development and is based on epidemiological, clinical, neuropsychological, biological and neuropathological markers (Sanches et al., 2008). Among these markers, neurological soft signs (NSS) are well studied in schizophrenia (Boks et al., 2000; Bombin et al., 2005; Compton et al., 2007; Mechri et al., 2008; Varambally et al., 2012, Romeo et al., 2014), but few studies have shown an interest to them in BD (Cermolacce et al., 2012).

Neurological Soft Signs (NSS) are minor neurological abnormalities including motor, sensory and inhibitory dysfunction (Zhao et al., 2013). They are non-specific indicators of organic brain lesion but they indicate a general dysfunction of the central nervous system (Bombin et al., 2005). NSS are well studied and overrepresented amongst patients with schizophrenia. however their specificity in this disorder remains controversial (Boks et al., 2000; Varambally et al., 2012; Zhao et al., 2013). Previous studies found an increase of NSS in bipolar patients (BP) compared with healthy controls. These findings could suggest that the NSS also constitute markers of vulnerability to BD (Negash et al., 2004; Goswami et al., 2006, Baş et al., 2015). However, to our knowledge, these markers have not been studied in unaffected relatives of BP. In addition, the relation between NSS and the severity of the disease, the functional impairment and the impact of treatment are not well clarified.

The objectives of this paper were to determine the prevalence, scores and sub-scores of NSS in a sample of bipolar I patients, compared to healthy siblings and controls and to explore the possible correlations with the socio-demographic and the clinical features of BP.

2. Methods

A case-control study was carried out in the psychiatry department in the Fattouma Bourguiba University hospital of Monastir

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http://dx.doi.org/10.1016/j.psychres.2015.11.047
0165-1781/

(Tunisia). All subjects were informed about the study procedures and gave their informed written consent before participating in the study.

2.1. Study population

2.1.1. Bipolar patients

The group of BP was recruited from outpatients with BD type I. A standardized interview performed on all patients by two senior psychiatrists (AMB and AM) confirmed that DSM-IV-TR criteria (American Psychiatric Association, 2000) for BD type I were fulfilled.

Inclusion criteria were a free consent to participate in the study, an age between 21 and 50 years and euthymia at the time of inclusion (Bech-Rafaelsen Mania Scale score <4 and Hamilton Depression Scale score <7) in order to get a homogeneous group.

Exclusion criteria were current substance abuse/addiction, history of neurological disease (Parkinson's disease), stroke, head injury, subarachnoid hemorrhage, epilepsy, attention deficit hyperactivity disorder, mental Retardation, learning disorders, motor disability or severe extra-pyramidal syndrome induced by neuroleptic treatment (Simpson-Angus Scale score >4). According to these criteria, 92 patients were included.

2.1.2. Healthy siblings and controls

The healthy siblings were recruited either when they came with the patient or after calling them by phone. For each patient, only one brother or sister was included in the study if he or she was available. The healthy controls were recruited among nursing and technical or security staff of the same hospital. For these two groups the inclusion criteria were: an age between 21 and 50 years, a free consent to participate in the study and an absence of psychiatric disorders, using the Mini-International Neuropsychiatric Interview (Lecrubier et al., 1997) by a senior psychiatrist (AM). The exclusion criteria were current substance abuse/addiction, history of neurological disease (Parkinson's disease, stroke, head injury, subarachnoid hemorrhage, epilepsy, attention deficit hyperactivity disorder, mental retardation learning disorders and motor disability), in addition to family history of psychiatric disorder for the control group. According to these criteria, 44 healthy siblings and 60 control subjects were included. Furthermore, 24 subjects were excluded during recruitment: 8 patients, 6 siblings and 10 controls.

2.2. Data collection

Data was collected by two junior psychiatrists who have received specific training before the study. The psychometric assessment was done by MWK and the NSS assessment was performed by IA.

2.2.1. Socio-demographic and clinical data

Assessment in bipolar I patients was made using medical records and interview with the patient and a member of his family if possible. The following data were collected: age; gender; marital status; school level; professional activity; family history of psychiatric disorder and its nature; age at onset of BD; duration of BD; number of hospitalizations in a psychiatric department; number, nature and severity of mood episodes; nature and severity of the last mood episode; current treatment. The same socio-demographic features were assessed in healthy siblings and controls.

2.2.2. Psychometric assessment

Bipolar I patients were assessed with the Bech-Rafaelsen Mania Scale (MAS) and the Hamilton Depressive Rating Scale (HDRS) (Guelfi, 1996) to confirm the euthymia at the time of inclusion.

The assessment of functioning level was made using the Global Assessment of Functioning (GAF) scale (Guelfi, 1996) which explores psychological, social and occupational aspects. It reflects the current need for treatment and has a prognostic value. A score superior to 70% was considered as a good global functioning.

2.2.3. Neurological assessment

The neurological assessment was performed using the scale of NSS validated by Krebs et al. (2000). This scale allows a standardized examination of 23 neurological signs, with four rating levels of 0–3, regrouped in five consistent factors: motor coordination (hand dysrhythmia, finger opposition, fist edge-palm, foot dysrhythmia, alternative movements: foot speed, alternative movements: hand speed, Standing heel-to-toe), Motor integration (Romberg, apraxia, Tandem walk, finger-to-nose, gait, tongue protrusion), Sensory integration (stereognosia, hand-face, constructive apraxia, graphesthesia, RL recognition), Quality of lateralization (RL confusion, lateral preference, RL asymmetry), and Involuntary movements (abnormal movement and posture, mirror movements).

2.3. Data analysis

Statistical analysis was performed using SPSS 11.0 software. To determine the prevalence of NSS, we chose a cutoff value of 11.5, obtained after ROC curve analysis performed in a population of 66 schizophrenic patients in Tunisia (Mechri et al., 2008). The NSS total score and sub-scores for each of the factors were calculated.

Factor sub-scores were computed by summing up the rating levels on the items loading on the respective factor. Given that the number of items differs between the five factors, we divided the sub-score of each factor by the number of items corresponding to that factor. The distribution of the variables was studied and parametric tests were used when these variables met the criterion of normality. Otherwise, non-parametric tests were also performed. ANOVA and Chi-squared tests were used for continuous and categorical variables, respectively. Differences in the NSS scores between the studied groups were tested by performing an ANOVA following by post hoc Tukey-test. The adjusted ANOVA was used if the age, gender or school level of the subjects differed between studied groups. Bonferroni corrections were applied to all post hoc analyses to adjust the multiple comparisons. The correlations between NSS scores and socio-demographic and clinical features of BP were calculated using Pearson correlation coefficients. A threshold of 0.05 was assigned for the significant associations. A multiple regression analysis of correlation between NSS total score (as dependent variable) and socio-demographic and clinical features of BP was performed using a forward stepwise method. The independent variables were those significantly associated with NSS in bivariate analysis and age and gender as potential confounding variables.

3. Results

3.1. Socio-demographic features (table 1)

The mean age of BP was 35.2 ± 9.3 years, and did not significantly differ from the healthy siblings and controls. Three quarters of BP were male and 58.7% of them were single with no significant difference with the comparison groups. BP had a mean school level of 9.3 ± 3.8 years, significantly lower than healthy siblings, and a professional activity in 73.9% of cases, which was significantly lower than other groups (Table 1).

Please cite this article as: Mrad, A., et al., Neurological soft signs in euthymic bipolar I patients: A comparative study with healthy siblings and controls. Psychiatry Research (2016), http://dx.doi.org/10.1016/j.psychres.2015.11.047