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ORIGINAL ARTICLE

Neuological Soft signs in euthymic bipolar I patients: State or trait markers.

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ABSTRACT

Background: Neurological soft signs (NSS) are endphenotypic markers widely studied in schizophrenia, but few papers have focused on evaluating them in bipolar disorder (BP) and their first degree relatives. ***Objectives:*** the aim of this study was to determine the prevalence and scores of NSS in bipolar I patients in remission state compared to their healthy relatives and controls, in addition to explore correlation with some sociodemographic data and clinical features of these euthymic patients. ***Methods:*** The study was conducted on 30 euthymic bipolar 1 patients, 30 their healthy relatives and 30 control subjects. The neurological soft signs were assessed by the Neurological Evaluation scale (NES). Bipolar I. Euthymic patients were also assessed by young Mania rating scale (YMRS) and the Hamilton Depression rating scale (HDRS). All subjects were recruited from Zagazig university Hospital. A simple questionnaire was structured for all participants to collect some sociodemographic data.***Results:*** NSS are prevalent in bipolar 1 euthymic patients and their first degree relatives, though significantly more in the affected patients.***Conclusion:*** This suggests that NSS could be considered as trait marker supporting the theory that bipolar disorder may be a neurodevelopmental disorder.

Keywords: Neurological soft sign; bipolar disorder; euthymic patients.

INTRODUCTION

Bipolar disorder (BD) is a significant cause of worldwide disability, an extremely common, often progressive disease with elevated treatment resistant, recurrence and chronicity rates, and linked with elevated suicide and medical comorbidity rates of premature mortality [1,2].

Despite various improvements in understanding bipolar disorder's etiology and underlying mechanisms, the results are still poor for many patients. As improvements can be produced with early managment, appropriate early detection techniques such as biological peripheral biomarkers need to be developed [3,4].

Neurological soft signs (NSS) are described as sensory and motor performance non-localizing defects recognized through clinical examination. NSS involves observable sensory integration (SI), motor coordination (MC), and complicated motor sequencing defects that do not indicate a particular neurological disorder. Previous biological studies have demonstrated that these soft signs reflect functional disorders in the brain[5,6].

Neurological soft signs are suggested as an significant clinical tool of defining a subgroup of patients with neurodevelopmental predisposing factors that may have genetic and environmental roots[7]. Most extensive research have shown a greater incidence of neurological defects in schizophrenic patients ; 92% of schizophrenic patients, 52% of patients with affective disorder and only 5% of control subjects have recorded neurological signs [8].

While NSS is the focus of a growing amount of schizophrenic research, comparatively few

studies tackle the problem of NSS in bipolar I disorder [9].

Identifying prospective biomarkers of bipolar disorder can help patients and their relatives in various ways. first The identification of disease markers, including NSS, can enhance diagnostic accuracy for BD and improve clinical interviews and observations. In addition, biomarkers may also be state-specific in particular for BD where disease may occur in depressed, manic or mixed states (state marker). Second NSS may play a part in primary prevention in at-risk individuals, with the advent of potential ' trait ' markers to recognize people at-risk[10].

Therefore, studying prevalence and scores of NSS in bipolar I disorder patients in remission state compared to their healthy relatives and controls, in addition to explore correlation with some sociodemographic data and clinical characteristics of these euthymic patients may boost our understanding of the causal mechanisms, neuroanatomy and pathogenesis of this particular disorder.

SUBJECTS & METHODS

A cross sectional case control neutralizing study was conducted in Zagazig University hospitals at the psychiatry Department. The study was conducted on 30 Egyptian subjects who were diagnosed to have bipolar I disorder in full remission (euthymic patients) (group A) and also conducted on another two groups , group B included healthy first degree relatives (30 persons) group C. included apparently healthy persons as control group (30 persons). Recruitment was conducted between 1 october 2017 to 31 December 2018 and subjects who met the following eligibility criteria at enrollment were invited to participate.1) Both sexes were included. 2) Age ranged from 20-50 years old. 3) patients fulfilling the Diagnostic and statistical manual of mental Disorders, 5th edition (DSM-5) criteria for bipolar 1 disorder in full remission 4) [11] All participants in the other two groups (B,C) will be matched for age, gender, social classes. we excluded subjects with: 1) Illiterate patients. 2) patients having history of medical or neurological disorders. 3) patients presenting during the acute stage of the illness. 4) First degree relatives have history of any medical , neurological or psychiatric disorders. 5) Refusal of participations. Ethical committee approval and written informed consent were obtained. All subjects were interviewed by a psychiatrist subjected to:

- **Collection of clinical and socio-demographic:** all subjects were interviewed by a psychiatrist using semi-structured questionnaire specially developed for this study (derived from psychiatric sheet of zagazig university hospital) as designed to collect socio-demographic data as age, sex, marital status, education, occupation , Age of onset of the disorder, duration of illness, Number of admission and number of manic or depressive episodes.
- **Psychometric assessment:** Bipolar I euthymic patients were assessed by both “Young Mania Rating Scale (YMRS)” [12] and “Hamilton Depression Rating Scale (HDRS)” [13] To confirm the euthymia at the time of inclusion
- **The Neurological Evaluation Scale (NES)** [14]: It is a structured instrument for the assessment of neurological soft signs. It includes representative items of sensory integration, motor coordination, sequencing of complete motor acts, and developmental reflexed. Each item is scored on a 3-point scale:0= no abnormality ; 1= mild but definite impairment ; and 2= marked impairment except for the snout, suck, and glabellar reflexes which are scored either as a 0 or 2.

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

- Statistical analysis was done using SPSS software version twenty five [15] . Data was presented in tables and figures.
- Quantitative data was showed as mean, median and range.
- Qualitative data was demonstrated as frequencies and relative percentages.
- Pearson’s chi square (χ^2) test was used to calculate difference between qualitative variables.
- One-way ANOVA (F-test) test was used to calculate difference between quantitative variables in more than two groups in normally distributed data.

- Kruskal-Wallis (KW) test was used to calculate difference between quantitative variables in more than two groups in not normally distributed data.
- Mann Whitney test (MW) was used to analyze continuous data between two groups.
- Spearman's correlation coefficient (r) was used to test correlation between BDNF and continuous variables.
- For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (P-value) and P value of <0.05 indicates significant results.

RESULTS

Table (1) shows that there was no statistical significant difference between the studied groups in demographic characteristics.

Table (2) shows that mean age of onset was 31.8 years old, mean disease duration was 4.7 years, mean duration of longest admission was 4.7 weeks, median number of previous episodes was 5, 93.3% of the studied patients had AP therapy and 90.0% had Lithium carbonate therapy.

Table (3) shows that there were statistical significant differences between the studied groups in Neurological soft signs.

Table (4) shows that there were statistical significant differences between Patients group and Relatives group in Neurological soft signs. Patients group had more NSS than relatives group.

Table (5) shows that there were statistical significant differences between Patients group and control group in Neurological soft signs. Patients group had more NSS than control group.

Table (6) shows that there were statistical significant differences between relatives group and control group in some Neurological soft signs. Relatives group had more NSS score than control group in Sensory integration, Motor coordination and total score.

Table (7) shows The NSS total score did not differ by gender: In addition, no difference was found in NSS sub-scores between male and female patients. Moreover, there was no correlation between the NSS total score and age, marital status and professional activity of BP. A negative correlation was found between the NSS total score and the educational level

Table (1): Demographic characteristics of the studied groups:

Variables	Patients group (n=30)	Relatives group (n=30)	Control group (n=30)	Test of sig.	P
Age (years):				f	
Mean ± SD	29.3 ± 3.7	31.8 ± 4.6	29.9 ± 3.5	2.7	0.1
Range	23.0 – 36.0	21.0 – 38.0	21.0 – 37.0		
Sex:				χ^2	
Males	16 (53.3%)	13 (43.3%)	15 (50.0%)	0.6	0.7
Females	14 (46.7%)	17 (56.7%)	15 (50.0%)		
Marital status:				χ^2	
Single	14 (46.7%)	10 (33.3%)	11 (36.7%)	1.8	0.9
Married	9 (30.0%)	11 (36.7%)	12 (40.0%)		
Divorced	6 (20.0%)	7 (23.3%)	6 (20.0%)		
Widow	1 (3.3%)	2 (6.7%)	1 (3.3%)		
Education:				χ^2	
Illiterate	0 (0.0%)	0 (0.0%)	0 (0.0%)	8.7	0.1
Elementary	1 (3.3%)	3 (10.0%)	3 (10.0%)		
Preparatory	5 (16.7%)	6 (20.0%)	5 (16.7%)		
Secondary	22 (73.3%)	12 (40.0%)	16 (53.3%)		
High education	2 (6.7%)	9 (30.0%)	6 (20.0%)		
Occupation:				χ^2	
Working	13 (43.3%)	16 (53.3%)	21 (70.0%)	4.4	0.1
Not working	17 (56.7%)	14 (46.7%)	9 (30.0%)		
Social class:				χ^2	
Low	13 (43.3%)	11 (36.7%)	10 (33.3%)	0.7	0.7
Middle	17 (56.7%)	19 (63.3%)	20 (66.7%)		

Table (2): Clinical characteristics of the studied patients:

Variables	Patients group (n=30)
Age of onset (years):	
Mean ± SD	31.8 ± 4.9
Range	22.0 – 42.0
Disease duration (years):	
Mean ± SD	4.7 ± 1.3
Range	3.0 – 7.0
Duration of longest admission (weeks):	
Mean ± SD	
Range	4.7 ± 0.9
	3.0 – 7.0
Number of previous episodes:	
Median	5
Range	3 – 7
Psychotropic therapy*:	
Anti-Psychotics	28 (93.3%)
Anti-Depressants	4 (13.3%)
Mood stabilizer drugs:	
Lithium carbonate	27 (90.0%)
Sodium valpronate	3 (10.0%)

* Two patients had both AP and AD therapies

Table (3): Neurological soft signs (NSS) of the studied groups according to Neurological Evaluation Scale (NES):

Neurological soft signs	Patients group (n=30)	Relatives group (n=30)	Control group (n=30)	KW	P
Sensory integration:					
Median	2.5	1	0	63.9	**<0.001**
Range	2 – 3	0 – 2	0 – 2		
Motor coordination:					
Median	2	0.5	0	41.3	**<0.001**
Range	0 – 3	0 – 2	0 – 2		
Motor sequencing:					
Median	1	0	0	23.1	**<0.001**
Range	0 – 3	0 – 1	0 – 1		
Developmental reflexes:					
Median	2	0	0	14.0	**<0.001**
Range	0 – 6	0 – 2	0 – 2		
Total score:					
Median	6	2	1	59.7	**<0.001**
Range	3 – 12	0 – 5	0 – 3		

Table (4): Comparison between Patients group and Relatives group in Neurological soft signs (NSS) according to Neurological Evaluation Scale (NES):

Neurological soft signs	Patients group (n=30)	Relatives group (n=30)	MW	P
Sensory integration:				
Median	2.5	1	6.5	**<0.001**
Range	2 – 3	0 – 2		
Motor coordination:				
Median	2	0.5	4.6	**<0.001**
Range	0 – 3	0 – 2		
Motor sequencing:				
Median	1	0	3.8	**<0.001**
Range	0 – 3	0 – 1		
Developmental reflexes:				
Median	2	0	2.5	**0.01**
Range	0 – 6	0 – 2		
Total score:				
Median	6	2	6.3	**<0.001**
Range	3 – 12	0 – 5		

Table (5): Comparison between Patients group and control group in Neurological soft signs (NSS) according to Neurological Evaluation Scale (NES):

Neurological soft signs	Patients group (n=30)	Control group (n=30)	MW	P
Sensory integration:				
Median	2.5	0	6.9	**<0.001**
Range	2 – 3	0 – 2		
Motor coordination:				
Median	2	0	5.9	**<0.001**
Range	0 – 3	0 – 2		
Motor sequencing:				
Median	1	0	4.2	**<0.001**
Range	0 – 3	0 – 1		
Developmental reflexes:				
Median	2	0	3.4	**<0.001**
Range	0 – 6	0 – 2		
Total score:				
Median	6	1	6.7	**<0.001**
Range	3 – 12	0 – 3		

Table (6): Comparison between relatives group and control group in Neurological soft signs (NSS) according to Neurological Evaluation Scale (NES):

Neurological soft signs	Relatives group (n=30)	Control group (n=30)	MW	P
Sensory integration:				
Median	1	0	2.5	**0.01**
Range	0 – 2	0 – 2		
Motor coordination:				
Median	0.5	0	2.2	**0.02**
Range	0 – 2	0 – 2		
Motor sequencing:				
Median	0	0	0.6	0.55
Range	0 – 1	0 – 1		
Developmental reflexes:				
Median	0	0	1.3	0.2
Range	0 – 2	0 – 2		
Total score:				
Median	2	1	2.5	**0.01**
Range	0 – 5	0 – 3		

Table7 : Correlation coefficients between total score of neurological soft signs and socio-demographic and clinical features of bipolar I patients

SocioDemographic and clinical features	Pearson coefficients
Age	- 0.14
Educational level	- 0.28*
Age at onset of BD	- 0.02
Duration of BD	- 0.11
Number of psychiatric hospitalizations	0.04
Number of mood episodes	0.04
Number of manic episodes	0.01
Number of depressive episodes	0.07

***P = 0.04 (Significant)**

DISCUSSION

While the sample of this research does not meet a community sample requirements, its epidemiological and clinical features may make it a representative sample for bipolar disorder.

The slightly bigger proportion of males than females (53.3 percent and 46.7 percent respectively) is very near to the usual frequency of mood disorders, as bipolar disorders are approximately equally common in males and females with a greater tendency towards hypomanic traits [16,17].

Most patients were either divorced or single (66.7 percent). Separate and divorced patients, either as a cause or as a consequence, have the largest rates of mood disorders. Presentation of patients in the unmarried single state can be explained by the early start of the disease which reduces their chance of being accepted for marriage due to the stigma of psychiatric disease [16,17]

The sample of this study showed a mean age at onset of the disorder of 31.8 years, which is consistent with recent studies. This, together with the mean duration of illness of 4.7 years and frequent hospitalization, gives an idea

about the burden of this disease on the patients and their families especially their caregivers [18,19].

Neurological soft signs (NSS) :

Some researchers propose that NSS reflects a failure in the integration within or between sensory and motor systems [20], while others argue for deficits in neuronal circuits involving subcortical structures (e.g. basal ganglia, brain stem and limbic system) [21]. Some NSS has been suggested reflecting a more general "latent" neurological dysfunction; their research reinforces the concept of NSS as a marker of disordered neurodevelopment [22].

Although the presence of NSS has been widely documented in schizophrenia, in bipolar disorder the same has not been achieved. In this research, bipolar patients showed a much worse performance on the NES than control topics; thus strengthening the hypothesis that NSS can play a part in early identification of the disease, acting as trait markers [22,23,24,25].

If these deficits were the phenotypic manifestation of genetic vulnerability to bipolar disorder, then healthy relatives (with genetic predisposition to bipolar disorder) would be anticipated to exhibit the same deficits, that would maintain the potential for bipolar disorder to be trait markers for NSS [26].

Compared to the control group, this study's first-degree relatives of bipolar probands showed a statistically significant worse achievement on NES in terms of total scores, motor coordination, and sensory integration scores. These results localize the neurological impairment found in relatives of bipolar disorder patients to the sensory integration and also to motor functions. However, in the total score of NES and all four subtest scores, bipolar patients showed significantly worse performance compared to their families. This decline may be the consequence of the disease process itself, or the medication's impact. However, the function of medication in neuronal circuit disruption is still not obvious except for the motor speed [27,28].

From the above results, we can deduce that bipolar disorder, which can be regarded as one of the neuro-developmental diseases, involves obvious neurological deficits in the neuronal circuits comprising the four categories of NSS, in particular the category of sensory integration that is the most stable and common abnormality among patients and their first-degree relatives. Thus, impairment of sensory integration (graphaesthesia, stereognosis, extinction, right-left confusion, and audiovisual integration) may be one of the neurological indications that will assist early detection of susceptible patients and high-risk relatives to develop bipolar disorder.

Gender and age differences in relation to NSS :

In this study, there was no statistically significant gender correlation with NSS prevalence. This may be incompatible with comparable research on schizophrenia and the first psychotic episode, considering male gender as a predisposing factor for NSS development in schizophrenic patients [21,29]. Also, there was no statistically significant relation between NSS and the age of patients, consistent with comparable NSS research in schizophrenia and psychosis [21,29]

NSS and Clinical Correlates :

There was no correlation between the total NSS score and the age of the patients in this research and in accordance with other studies[30,31]. Neuroimaging research However, a adverse correlation was discovered between BP age and gray matter volume. [32,33] These modifications in histopathology could explain the earlier reported rise in NSS by age [34].

No significant correlation existed between total NSS score and gender. Similar findings were recorded [30,31]. In female bipolar and schizophrenic patients, however, greater NSS scores were discovered. [35] Gender influence on NSS frequency in BP appears to be poorly studied and the findings are contradictory and inconsistent.

In this study, patients with fewer years of education had significantly higher scores of NSS which is in agreement with other studies.[35]

However, **Negash A, et al (2004)** have not found such a correlation[31]. Generally, educational failure in BP would be related to

cognitive dysfunction rather than to pre-morbid intellectual deficit. [31,36]

Low-educational patients had significantly greater NSS scores. Similar results have been found. [35] However, this correlation has not been discovered [31]. In BP, low educational level would generally be associated with cognitive dysfunction rather than pre-morbid intellectual deficit [36].

No correlation was found between age at onset of BD and the score of NSS, which is consistent with the results of the only study that evaluated this association. [37] This describes the lack of correlation between the NSS and disease length. However, after two to four years of BD evolution, other trials revealed a reduction in NSS results. [38,39] In essence, the improvement involved the sensory integration sub-score associated to improving mood symptoms [39].

No correlation existed between NSS score and mood episodes criteria. However, correlations between these state markers and trait markers such as the NSS are difficult to conclude. No correlation was discovered with either the number of episodes or their severity in line with this research [31].

NSS scores did not differ between patients whether treated by antipsychotics or not. This finding is in agreement with results of other studies [30,31]. Indeed, NSS are present in patients who have never been treated with anti- psychotics and are not induced by antipsychotic medication [33,40].

LIMITATIONS

There should be some limitations in our research. First, BP recruitment occurred solely in an outpatient psychiatric department and at the moment of incorporation they had to be euthymic. They may not generally represent the NSS frequency in BP. Furthermore, because there was a male predominance, our sample cannot be representative of BD. This can be clarified by a selection bias because in our psychiatric department male patients were more recruited. Second, using only hospital employees as healthy controls can result in a bias in selection. Also, because of the lack of patients on monotherapy, it was difficult to demonstrate the impact of each drug on the NSS individually. It must be acknowledged that examining drug-free patients is the most methodologically efficient method. However, it is highly uncommon to discover patients with proven bipolar disorder who are medication-free in clinical practice.

CONCLUSIONS

In conclusion, the excess of NSS in bipolar patients and their healthy siblings, particularly motor and sensory signs, may suggest that these defects are markers of BD vulnerability. In addition, motor and sensory signs are unrelated to clinical characteristics in patients with bipolar I disorder. These findings favor motor and sensory deficits as part of bipolar I disorder, so NSS could be regarded as a trait marker that supports the hypothesis that bipolar disorder could be a neurodevelopmental disorder.

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