Neurological Soft Signs: A Further Step in the Diagnosis of Bipolar-I Disorder

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Objectives: To study the prevalence and demographic characteristics of Neurological Soft Signs (NSS) among the patients with Bipolar Mood Disorder-I (BID).
Method: In a cross- sectional descriptive-analytic study we studied 20 patients with BID with BID with 20 healthy individuals. We used DSM-IV and Young Mania Rating Scale (MRS) for diagnosing and rating the patients with BID, Neurological Evaluation Scale along for assessment of NSS.
Control subjects who were matched on age and sex were selected; other confounding factors such as age at the onset, severity and duration of the disease were also considered and analyzed to find any possible correlation with NSS.
Results: Total NSS scores were significantly higher in the patients' group (PV<0.0001). The most significant difference in NSS subscales was detected in the Sequencing of Complex Motor Acts (PV<0.0001). No significant correlation was found between NSS scores and age at the onset of the disease, severity and duration of the disease and medication.
Conclusion: This study may emphasize the role of NSS as a sign of organic brain disorder which may be present independent of medication effects in the patients with BID; however, further studies may be able to extend our findings to explore the etiology and pathogenesis of BID.

Keywords:
Bipolar- I Disorder, Neurological Soft Signs, Neurological examination

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A long time has passed since the term "Neurological Soft Signs (NSS)" has entered the medical literature" by Loretta Bender in 1940 (1). Afterwards, other studies have been done on NSS in other psychiatric disorders such as first episode psychosis, and schizophrenia (2). It has been shown that the prevalence of NSS is higher in first episode psychosis and in medication naive schizophrenia patients (2, 3). However, less attention has been paid to mood disorders.

It is believed that Neurological Soft Signs are reflections of functional disorders in the selective parts of the brain; and the previous belief that these signs only indicate diffuse brain dysfunction do not seem to be correct (4). Recent studies have supported the idea that NSS may be related to a specific deficit in the function or anatomical regions of the brain (5, 6). This is why scientists assume that these signs can be used as a bridge to connect neurology and psychiatry. More than half a century after NSS's first definition, at this time, the role of NSS is more important in elucidating the etiology (7), prognosis (8), differential diagnosis (6, 7) and even prediction of the response to treatment (9, 10) in different psychiatric disorders.

Biological factors such as neurochemical and hormonal imbalance, genetic factors and psycho-social mechanisms so far have been known as the etiology of BID. Furthermore, neuroanatomical and neurophysiological etiological factors refer to the localization of the specific regions in the brain (11). It has been found that BID was related to anatomic abnormalities in the medial temporal lobe, especially in amygdale, prefrontal cortex and cerebellum (12).

Instead of relying on advanced technology which demands exorbitant expenses and highly-trained staff, we focused on a feasible clinical method by comparing NSS in BID patients and controls in order to assess our main hypothesis which implies that NSS are more prominent in the patients with BID than normal subjects. Other adjunct goals of this study were to evaluate the possible correlation between characteristics of the disease including severity, age at the onset and duration of the disease, with total NSS score. The effect of medications used regularly to control the disease on the NSS was also assessed as a probable confounding factor.

Materials and Method

Twenty patients diagnosed with BID by two psychiatrists (convenience sampling) according to DSM-IV criteria were selected from those admitted to Roozbeh Hospital (13). All were between 15 and 45 years of age. The exclusion criteria, all of which can affect NSS and confound the results, were disorders other than BMD-1 in axis I or II, major neurological disease or the existence of Neurological Hard Signs, taking medications not related to their disease, history of head trauma with unconsciousness, epilepsy, amnesia or a required surgery, being hospitalized in a psychiatry hospital for more than 6 consecutive months (admission for BID was an exception) and addiction to alcohol or drugs. Written informed consent was obtained from all the participants .

The Control group included 20 healthy volunteers who worked as the hospital staff, matched for sex ratio and level of education, with no psychiatric and/or neurological complaints.

In order to assimilate the cases and controls and also to prevent possible biases, every single subject of the control group was matched to a patient in the case group with respect to age and sex. The age difference of less than five years was ignored. It is notable that factors likely to violate the results were considered as exclusion criteria in the control group ; and they are as follows: having had any disorder in axis I or II; any mood, neurological or cognitive disorder in first degree relatives; positive medical history of major head trauma; addiction to alcohol or drugs and any regular drug usage .

To rate the severity of the disease in patients we used YMRS (Young Mania Rating Scale). It was first introduced by Young et al. in 1978 (14) and is a scoring system consisting of 11- item- characteristics of the manic episode with minimum and maximum scores of zero and 60 respectively .

NSS were evaluated by NES (Neurological Examination Scale) which was invented in 1989 by Buchanan and Heinrich (5). NES is now the most commonly used scale for the assessment of NSS with validated categories of NSS in terms of internal consistency (2). NES consists of 26 independent tests; thirteen of which are categorized in three functional subscales (Table 3). The possible minimum and maximum NSS total scores are 0 and 52 respectively. Cerebral dominancy was determined by assessment of handedness as a part of the NES.

The selected patients were first interviewed and in order to measure the severity of the disease, they were given a Mania Rating Scale (MRS) score. Then they were examined for NSS according to NES.

The controls were only assessed for NSS according to NES. Since the patients could not be asked to stop taking their medications- even temporarily- and these medications may affect some of categories of NSS ex. Coordination. We also tried to consider the analysis to assess any possible relationships between medication and NSS.

Therefore, we managed to categorize the type of medications into two main groups according to their pharmacological properties: 1) antipsychotic, anti-epileptic with mood stabilizing effects and 2) Lithium. The probable effect of each category on NSS was evaluated independently. Inspired by similar studies, we compared all medications in each category to one representative drug according to their equivalent dosage. Then the relationship between the total NSS score and the dose of medication was evaluated for each drug category independently.

Since the obtained data from the NES were discrete and did not have a normal distribution, Kruskal-Wallis statistical test was used to compare the NSS scores between the cases and controls. In order to determine the correlation between the severity, duration and age at the onset of the bipolar disease and the total NSS score, the Spearman test was used. This test was also used to analyze the effect of medications in each drug category on NSS.

Results

The demographic results can be found in Table 1.The MRS score acquired by the patients ranged from 7 to 41 with an average score of 19.3. No significant relationship could bewas found between the severity of the disease and the total NSS score ($p=0.6306$, spearman $r= -0.1145$, $t (N-2) =0.4891$). The age of the onset of the disease had no significant relationship to with the total NSS score neither ($p= 0.1454$, Spearman $r=0.5373$, $t (N-2) =2.7034$). It was the same with the duration of the disease; no significant correlation was found between the duration of the disease and the total NSS score ($pe= 0.3497$, Spearman $r=0.2207$, $t (N-2)= 0.9600$).

The three categories of medication did not seem to affect the total NSS score significantly (for antipsychotics: $p = 0.4921$, spearman $r=-0.1630$, $t(N-2) =-0.7012$, for antiepileptics: $p=0.8296$, Spearman $r=-0.0514$, $t (N-2)=-0.2183$ and for Lithium: $p = 0.8455$,

Table 1- Demographic findings in Patients with BMD-I and control group subjects

	Cerebral dominance		Age distribution						Duration of the disease				Pos. FH	Med. use
	R	L	< 21	21-25	26-30	31-35	36-40	> 40	1st episode	<11yrs	11-20	>21 yrs		
Patients	3	17	0	4	4	3	2	7	4	9	6	1	6	15
Controls	2	18	2	4	1	4	4	5	-	-	-	-	-	-

Pos. FH: Positive Family History. Med: Medication

Table 2- kruskal-wallis statistical test on NES subscales comparing patients and control group

Subscale	Ave. Rank		P Value	Z	Absolute Difference
	Patients	Controls			
Integrative Sensory Dysfunction	26.4	14.6	0.001	3.19	11.8
Motor Incoordination	29.1	11.9	0.0001	4.64	17.2
Sequencing of Complex Motor Acts	30.5	10.6	0.0001	5.38	19.9

Table 3- NES tests results in patients compared to control group using kruskal-wallis statistical test

Test name	Impaired (%)		Ave. rank		P value	Z	Absolute difference
	Patients	Controls	Patients	controls			
Sensory Integration							
Audiovisual Integration	60	25	24.1	16.9	0.53	1.93	7.2
Stereognosis	5	0	21.0	20.0	0.787	0.27	1.0
Graphesthesia	30	0	23.5	17.5	0.105	1.62	6.0
Extinction	20	0	22.5	18.5	0.279	1.08	4.0
Right-Left Confusion	50	10	24.8	16.3	0.021	2.30	8.5
Motor Incoordination							
Rapid Alternative Movements	35	0	24.0	17.0	0.058	1.89	7.0
Tandem Walk	45	0	25.0	16.0	0.015	2.43	9.0
Finger-Thumb opposition	65	0	26.0	15.0	0.003	2.98	9.0
Finger to Nose test	15	0	22.0	19.0	0.417	0.81	3.0
Rhythm Tapping	65	10	26.4	14.6	0.001	3.21	11.8
Sequencing of Complex Motor Acts							
Fist-Ring test	100	55	29.4	11.6	0.0001	4.81	17.8
Fist-Edge-Palm test	100	40	29.9	11.1	0.0001	5.09	18.8
Ozeretski test	90	10	29.3	11.8	0.0001	4.73	17.5
Other tests							
Adventitious Overflow	5	0	21.0	20.0	0.787	0.27	1.0
Romberg Test	20	0	22.5	18.5	0.279	1.08	4.0
Tremor	25	0	23.0	18.0	0.176	1.35	5.0
Memory	90	30	28.4	12.6	0.0001	4.27	15.8
Mirror Movement	15	45	18.4	22.7	0.245	1.16	5.7
Synkinesis	55	15	24.7	16.3	0.022	2.29	8.4
Convergence	70	10	27.0	14.1	0.0001	3.49	10.9
Gaze Impersistence	30	0	23.5	17.5	0.105	1.62	6.0
Glabellar Reflex	60	10	26.0	15.1	0.003	2.95	10.9
Snout Reflex	0	0	20.5	20.5	1.000	0.00	0.0
Suck Reflex	25	0	23.0	18.0	0.178	1.35	5.0
Grasp Reflex	10	5	21.0	20.0	0.787	0.27	1.0

Spearman r= 0.0465, t (N-2) =0.1976).
The total NSS score, ranged from 6 to 30 in the patient group with an average of 18.55, whereas it ranged from 0 to 6 in controls with an average score of 2.90. The total NSS score was significantly higher in the patients compared to the controls (p=0.0001, z= 5.40, absolute difference= 20.0).
Functional subscales of NSS and their relative comparison have been shownare demonstrated in Table 2 in detail.
As demonstrated, sequencing of complex motor acts is the most impaired subscale among the patients. Impairment frequency of each individual NSS test in patients is included and compared with the controls in table 3. According to this Table, the most frequent NSS in the patients are as follows: Fist-edge-palm test, Fist-ring test and Ozeretski test.
Applying Kruskal-wallis statistical test, the eleven statistically significant NSS were found to be as follows: Fist-edge-palm, Fist-ring, Ozeretski, Memory, Rhythm tapping, Convergence, Glabellar reflex, Tandem walk, Finger-thumb opposition, Right-left confusion, Synkinesis (Table 3).

Discussion

Concerning the main hypothesis of this study, we found a significant difference between the patients and the age and sex matched controls in terms of the total NSS score. Comparing our findings with that of Nasrallah et al which focused on evaluating the NSS in patients with BID and schizophrenia, using PANESS and comparing them to the controls in 1983, both studies showed a significant difference in total NSS scores between the patients with BID and controls regardless of the scale used (7). Presence of neurological signs in patients diagnosed as BID has been reported by other researchers (4, 15, 16). Goswami and Moore et al. found that soft signs occurred even in patients with bipolar disorder who are in euthymic phase; therefore, it may represent trait deficits (17). Basu et al reported similar findings in adolescents diagnosed as bipolar disorder (18 .(
These findings seem to point to the involvement of several specific pathways in NSS rather than the involvement of a specific brain structure or CNS dysfunction. The first dimension mainly consists of coordination tasks and seems to reflect fronto-cerebellar dysfunctions. Similar findings have been reported by Boks et al on patients with first episode schizophrenia and depression (2). Boks pointed to the researches which had confirmed the role of cerebellum in cognitive functions and its impairment in schizophrenia and depression (2). Our results seem to support the evidence for cerebellar involvement in BID.
As shown in table 2, another subscale with the most significant difference is the Sequencing of Complex Motor Acts. It is notable that in a similar study on BID patients in 2004, sequencing of complex motor acts was found to be the most impaired subscale as well (16). Boks et al (2004) compared patients with first-episode schizophrenia, clinical depression and healthy controls. They found that patients with schizophrenia showed more abnormalities in movement disorder dimensions of neurological examination (2); "However, patients with schizophrenia were compared to the mood disorder subgroup that were not necessarily suffering from psychosis and this may have biased their findings" (19). In contrast with these findings, Whitty et al (2006) didn't find significant differences in prevalence of NSS among patients with bipolar I disorder, schizophrenia or other forms of psychosis (19). The findings support the view that different forms of psychoses share epidemiological and neuropathological characteristics and there are no individual or categories of NSS to help us to differentiate various diagnoses of psychosis (19). Therefore, it may be compatible with Witty et al who concluded that "major psychoses share common etiological antecedents and may not be discrete disease entities" (19 .(
If we refer to Cox and Ludwig's study in 1979, who tried to correlate the soft signs to various parts of the brain, we might be to localize the three tests with the most significant differences (Fist-edge-palm, Fist-ring and Ozeretski) to the parietal lobe. The two following tests (memory and rhythm tapping) might also be related to the temporal lobe. Some researchers have found that most of the soft signs found in patients with bipolar disorder are related to parietal and temporal lobe dysfunction (4). One study in 1998 by Starkstein, Boston and Robinson on patients with head trauma had shown that right unilateral lesions, especially in the frontotemporal areas can cause Manic features (20). Medial temporal lobe hypoplasia was found in patients with bipolar I disorder (similar to that seen in schizophrenia) and it was found to be correlated with some degrees of cognitive impairment (4, 21). Therefore, the neurological signs in patients with BID may reflect pathological changes in brain structure that have roles in abnormal cognition and behavior as well as impairment in motor coordination, sequencing, and sensory integration (4 .(
Statistical analysis did not show any correlation between the severity of the disease and total NSS score. However in a study by Praharaj et al, "There was a significant positive correlation of neurological scores including total score, filtered score, soft signs , motor coordination and cognitive domain with the YMRS score, implying that neurological abnormalities increase with the severity of mania" (4). Basu et al found similar findings (4, 18). However, studies on patients with first-episode psychoses have not found such an association (Emsley et al., 2005; Chen et al., 2005) (19). Moreover, Sanders et al. (1994) and Johnstone et al. (1990) didn't find a relationship between NSS and global assessment of functioning (GAF) or occupational outcome (19). It has to be mentioned as our limitation that the patients in our study were at different stages of their disease during

the time of evaluation. Manic episodes can affect some tasks which are needed to be done in NES, thus, investigating whether these neurological abnormalities are state or trait markers is needed .

There was no significant correlation between the age at the onset of the disease and total NSS score. This finding should be interpreted with caution as the correlation coefficient is calculated about 0.5 which is not very small (probability of type II error) and the finding isn't consistent with a study done by Björck et al who reported that patients with early onset schizophrenia may perform worse than late-onset patients in motor coordination tasks at the onset, but the age-dependent deterioration of motor coordination may be more rapid in late-onset patients (22). Nevertheless, in a more recent study on patients with schizophrenia, no correlation was observed between age and any categories of NSS (2). More studies on larger sample sizes accompanied by higher power may be helpful to find a correlation between age at the onset and NSS. Moreover, in order to achieve a more reliable conclusion on the correlation between the duration of the disease and total NSS score in patients with BID, longitudinal studies need to be conducted. Few studies have prospectively evaluated whether NSS are progressive, static or remediable with effective treatment. Some studies concluded that NSS fail to improve significantly over the early course of illness. The patients' follow ups with first episode psychosis in a prospective study showed that there was a statistically significant improvement in neurological function. A significant association at first episode and in the follow-up was found between NSS and psychopathology especially for patients with schizophrenia (19). Persistent neurodysfunction at first episode was related to persistent negative symptoms and was associated with worse outcome (19.(

Since the patients were all taking various drugs from each category due to their different clinical backgrounds, the data are incomparable unless we could find a way to assimilate them. It should be emphasized that the main focus of our study has not been the effect of medication and the analysis was only done to consider a probable confounding factor. In our study, increasing the doses of medications did not worsen NSS (no correlation between the doses of three clusters of drugs and total NSS score was found). Previous studies on schizophrenic patients have shown no significant correlation between medications and NSS score (23, 24). In a review by Heinrichs and Buchanan, they concluded that medications didn't change neurological signs in patients with schizophrenia in most studies (4, 25). In the study conducted by Praharaj et al, neurological abnormalities were examined in 30 drug-free patients and 30 drug-treated patients with BMD. He pointed that "the presence of neurological signs in drug-free patients suggests that neurological abnormalities occur independently of medication effects" (4). In the drug treated groups, they found no significant differences in neurological signs among patients receiving different medications with the exception of the sensory domain score which was higher in patients receiving mood stabilizers (4). Further studies in different areas such as electrophysiology, neuroimaging, neuropathology and neurophysiology are needed.

We conclude that NSS differs significantly between patients with BID and normal population. Our finding confirms the findings of previous studies which indicate an organic basis and presence of neurologic abnormalities in the patients with BID. Therefore, neurological soft signs may be used as an organic indicator in these patients. However future studies employing concurrent neurological examminations and volumetric structural and functional neuroimaging should further elucidate these issues.

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