

Neurological soft signs in psychoses. II: an explorative study of structural involvement amongst drug naive first episode patients

Abstract

Background: The aims and objective of the study was to find out the different structural involvement in the three study groups, namely brief psychotic disorder, schizophreniform psychosis, and schizophrenia as reflected by the neurological soft signs (NSS). **Material and methods:** The study was conducted in the Department of Psychiatry, Silchar Medical College and Hospital, Silchar, Cachar, Assam. In this study, we had further classified the soft signs into groups related to their corresponding brain structures as per the aims and objectives. **Results:** Our study consisted of 30 patients distributed into three case groups, namely brief psychotic disorder having 14 cases, schizophrenia having 12 cases, and only four cases in the schizophreniform group. We have made a novel attempt to establish a functional relationship between the structural involvement and the three groups of disorders under study through the evaluation of NSS at the onset of symptoms, which at times may not be possible to diagnose through currently available radio-imaging techniques. We have definitely found a predominant involvement of the cerebellum in the brief psychotic disorder and schizophrenia groups, and the involvement of parietal lobe in the schizophreniform psychosis group; although the results were not statistically significant. **Conclusion:** We hope that in future larger studies with more number of patients will shed definite lights in the present study findings.

Keywords: Brief Psychotic Disorder. Schizophreniform Psychosis. Schizophrenia.

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Introduction

Definition

Shaffer *et al.*[1] defined neurological soft signs (NSS) as a non-normative performance on a motor or sensory test identical or akin to a test item of the traditional neurological examination, but a performance that is elicited from an individual who shows none of the features of a fixed or transient localisable neurological disorder. Again Kolakowska *et al.*[2] conceptualised NSS as a non-specific marker of vulnerability to psychosis or a factor, which modifies the clinical course. They proposed that a collection of aetiologic significance indicating a discrete organic subtype of the illness. Although the presence of NSS has been documented extensively in schizophrenia as a whole, the same cannot be said for patients undergoing their first psychotic episode.

Historical background and origin of NSS

The possibility for the origin of neurological abnormalities is that it results from some early acquired lesion, i.e. it represents a feature of brain damage. This suggestion was made by Prechtl and Stemmer,[3] and later advanced by Gubbay *et al.*[4] However, these studies were not inferential.

Shaffer *et al.*[1] examined this hypothesis using comprehensive obstetric records of traumatic deliveries, prenatal haemorrhage, or pre-eclamptic toxemia, and found there was a significant excess of low birth weight for gestation among males with neurological abnormalities at the age of seven. Another study conducted by collecting obstetric records of patients and their siblings found that obstetric complications were significantly increased in patients but not in siblings compared to their respective neonatal controls.[5] However, there was a lack of significant relationship between neurological impairment and obstetric complications in the patient group, and therefore, concluded that besides perinatal events, there are other determinants of neurological abnormality in schizophrenia.

These studies indicate a higher rate of neurological abnormalities characterising a portion of the offspring's and relatives of patients with schizophrenia who would assume to be at a higher risk to develop schizophrenia on a genetic basis. This is compatible with the view that neurological signs reflect a familial transmitted alteration in neurological process that constitutes a vulnerability or diathesis to subsequent schizophrenia.

Types of NSS

NSS suggest abnormality in various functional systems which can be evaluated under the following types.

Sensory integration: Audio-visual integration, stereognosis, graphaesthesia, extinction, right-left confusion.

Motor coordination: Tandem walking, rhythm tapping, finger-thumb opposition.

Motor sequencing: Fist-ring test, fist-palm-edge test, Ozeretzki's test.

Primitive reflexes: Palmomental, grasp, snout, gaze, sucking reflexes, etc.

Studies have supported the idea that NSS may be related to specific deficit in the functional or anatomical regions of the brain,[6,7] for which scientists in the present day assume that these signs can be used as a bridge to connect neurology and psychiatry.

Significance of NSS

The clinical importance of soft signs is not in any impairment of motor or sensory function associated with their presence, for there does not seem to be any, but in their value as an indicator of some central nervous system (CNS) factor, that might have casual or predictive value for associated psychological dysfunction, and in particular, learning and/or psychiatric abnormalities.[1] Although the clinical significance is unclear, NSS are regarded as an indicator of non specific brain damage and their presence reflects dysfunction in various integrative functions that cannot be localisable to a specific brain structure. Positive relationship for the occurrence of NSS in various conditions predicts the underlying importance of these as a state or trait marker. The association of NSS with premorbid antisocial traits, prominent negative symptoms,[8,9] cognitive impairment,[10] ventricular enlargement,[11] obstetrical complications[12] are some indications of NSS as state and trait marker.

NSS in general medical conditions

NSS is an important test which is used in patients without focal neurological findings to express various functional impairments of the brain system. NSS have been extensively studied in various psychiatric conditions like schizophrenia, obsessive-compulsive disorder, and a high prevalence is being reported.

Gilles de la tourette syndrome is a childhood onset neuro-psychiatric disorder characterised by multiple motor and vocal tics, and has been found to be associated with electroencephalographic (EEG) abnormalities, NSS, and low performance intelligence quotient (IQ) results.[13]

Neurological deficits reflecting cerebral degeneration are not uncommon in patients with Alzheimer Disease (AD); with increasing cortical atrophy, neurological signs become more prevalent. Focal neurological signs such as pyramidal signs which represent localised brain lesions are commonly found in patients with vascular dementia. However, soft

neurological signs indicating diffuse brain damage are likely to be present in AD and their severity may be indicative of disease progression.[14]

NSS in psychiatric conditions

High incidence of NSS have been reported in minimal brain dysfunction,[15] emotionally unstable character,[8] hysteria,[16] heavy poly drug users,[17] and consistently so in schizophrenia.[18] Rochford *et al.*[19] and Cox and Ludwig[7] studied patients with alcoholism, unipolar depression, bipolar illness, schizophrenia, and mixed neurotic disorders; among which, NSS were significantly present in schizophrenia.

NSS in first episode psychosis

Various studies conducted on NSS on psychiatric illness such as schizophrenia and first episode psychosis have reported a higher prevalence.[20] Investigating these patients at an early stage of the illness has the following potential advantages like it can clarify whether NSS are part of neurodysfunction that underlies schizophrenia rather than consequence of degenerative processes and it can elucidate whether or not they are simply a neuroleptic-induced epiphenomena, i.e. a consequence of long-term pharmacological treatment.

Lawrie *et al.*[21] found excess of NSS in first episode psychosis compared to high-risk asymptomatic subjects which in turn showed greater NSS pathology than healthy subjects. These findings suggest that neurological dysfunction observed in first episode patients is at least in part related to the pathogenesis underlying the illness and can be observed in association with an increase risk of the disorder even before the onset full-blown psychotic illness.

NSS in drug naïve psychosis

One area of interest in the study of neurological abnormalities has been the role of medication in the expression of neurological abnormalities. The excess of NSS in schizophrenia and various other forms of psychosis has been demonstrated, and also of their presence in first episode of the illness. Therefore, it becomes important to know whether medications have some influence on the status of NSS.

Neurological impairment may be associated with the prognosis of the disease and when associated with poor prognosis, patients tend to receive higher antipsychotic doses and therefore could drive the association between neurological signs. Similarly, it is found that more severe neurological impairment is associated with poorer antipsychotic response and again there could be a trend for more neurologically impaired patients to be on higher doses.

The view that NSS are independent of antipsychotic treatment and not state dependent is supported by studies of antipsychotic naïve patients. Although a few studies were unable to exclude the influence of medication in the appearance of neurological abnormalities,[8,22] Heinrich and Buchanan[6] conclude that medications do not seem to alter the neurological signs in most cases.

NSS as trait and state marker

Soft neurological signs represent a potential intermediate phenotype because they suggest evidence of brain dysfunction and are not dependent on the patients' motivation and understanding instructions. Soft signs have features that are characteristics of useful intermediate phenotypes. These signs appear trait-like in that they are relatively stable over time which is advantageous for genetic studies. The relationship between NSS and diagnosis could improve our insight in possible underlying neuropathology, and therefore need further research to investigate the specificity of NSS in various psychiatric disorders.

Importance of the present study

The present study tried to find out the correlation between NSS and functional impairment of different brain structures specifically related to particular soft signs which would indicate the prominent areas of dysfunction and that in the long run may help to evaluate strategies to minimise them.

Aims and objectives

1. To see the associations between NSS and important socio-demographic variables
2. To find out the different structural involvement as reflected by the NSS amongst the three study groups consisting of patients with brief psychotic disorder, schizophreniform psychosis, and schizophrenia.

Method and materials

Method and materials are described elsewhere.[23] In this study, we had further classified the soft signs into groups related to their corresponding brain structures as per the aims and objectives. Inform consent was taken from each subject along with that of their close attendants. The study was approved by the Institutional Ethical Committee.

Statistical analysis

Data were analysed by chi-square test.

Results and observations

Socio-demographic variables of the patients were presented elsewhere.[23]

Associations between NSS and important socio-demographic variables

Table 1 shows the detail distribution of cases in the 16 items of the Heidelberg Manual (types of NSS) among the three groups of disorders under study and their relation to the three different age groups. In our study, from the 15-24 age group, 10/10 cases showed impairment in diadochokinesia, followed by 9/10 cases showing impairment in finger-nose test, right/left orientation, Ozeretzki's test, fist-edge-palm test, and pronation-supination, while only 1/10 patient showed impairment in tandem walking, two point discrimination, and face-hand test. From the 25-34 age group, 15/15 patients showed impairment in right/left orientation, Ozeretzki's test,

fist-edge-palm test, and speech and articulation, followed by 14/15 cases showing impairment in diadochokinesia and stereognosis, and only 1/15 cases showing impairment in two point discrimination and face-hand test, and no impairment was found in tandem walking in this group. And from the 35-50 age group, 5/5 patients showed impairment in diadochokinesia, right/left orientation, pronation-supination, and speech and articulation, while no impairment was found in tandem walking and face-hand test in this group. Statistical analysis of the above data was done using the chi-square test. The results of the data however did not show a significant association.

Figure 1 shows the distribution of cases in the three different age groups in relation to the types of NSS.

Table 2 shows the detail distribution of cases in the 16 items of the Heidelberg Manual (types of NSS) among the three groups of disorders under study and their relation to their gender. From this table, we find that the commonest NSS in the male group was diadochokinesia, right/left orientation, Ozeretzki's test, fist-edge-palm test, and speech and articulation (18/19), followed by finger-thumb opposition and pronation-supination (17/19), while in the female, the commonest NSS was diadochokinesia and right/left orientation (11/11), followed by Ozeretzki's test, fist-edge-palm test, pronation-supination, and speech and articulation (10/11), showing no significant differences between the two groups. The statistical analysis also found the association to be insignificant.

Figure 2 shows the distribution of the cases among the male and female gender, and in relationship to the types of NSS.

Table 3 shows the distribution of the cases and total NSS scores as per severity of neurological impairment among the three different age groups. In our study, 6/10 cases from the 15-24 age group and 9/15 from the 25-34 age group had mild impairment, while only 1/5 cases from the 35-50 age group had moderate impairment. No obvious differences were noted in relation to the severity of NSS and different age groups so far the numbers of cases are concerned in relation to their total number in each group. However, statistical analysis done with the total NSS score, (not the no. of cases) has found a significant relation with the different age groups.

Figure 3 shows the distribution of the cases according to the severity of NSS in relation to the three age groups.

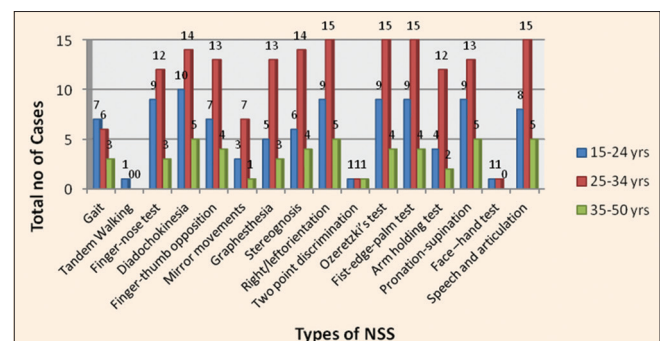


Figure 1: Types of NSS in relation to age in years. NSS=Neurological soft signs.

Table 1: Types of NSS in relation to age in years

Heidelberg manual items	Age											
	15-24 (n=10)				25-34 (n=15)				35-50 (n=5)			
	BPD	SP	SC	Total	BPD	SP	SC	Total	BPD	SP	SC	Total
Gait	4	1	2	7	1	2	3	6	3	0	0	3
Tandem walking	0	0	1	1	0	0	0	0	0	0	0	0
Finger-nose test	5	1	3	9	3	3	6	12	2	0	1	3
Diadochokinesia	6	1	3	10	4	3	7	14	4	0	1	5
Finger-thumb opposition	3	1	3	7	3	3	7	13	4	0	0	4
Mirror movements	1	0	2	3	2	2	3	7	0	0	1	1
Graphaesthesia	2	1	2	5	3	3	7	13	2	0	1	3
Stereognosis	3	1	2	6	4	3	7	14	3	0	1	4
Right/left orientation	6	1	2	9	4	3	8	15	4	0	1	5
Two point discrimination	0	0	1	1	0	0	1	1	1	0	0	1
Ozeretzki's test	5	1	3	9	4	3	8	15	4	0	0	4
Fist-edge-palm test	5	1	3	9	4	3	8	15	4	0	0	4
Arm holding test	2	1	1	4	2	3	7	12	2	0	0	2
Pronation-supination	5	1	3	9	3	3	7	13	4	0	1	5
Face-hand test	0	0	1	1	0	1	0	1	0	0	0	0
Speech and articulation	5	1	2	8	4	3	8	15	4	0	1	5

$\chi^2=9.672$, $df=30$, and $P<0.9998$, NSS=Neurological soft signs, BPD=Brief psychotic disorder, SP=Schizophreniform psychosis, SC=Schizophrenia, df =Degree of freedom

Table 2: Types of NSS in relation to gender

Heidelberg manual items	Gender							
	Male (n=19)				Female (n=11)			
	BPD	SP	SC	Total	BPD	SP	SC	Total
Gait	3	3	5	11	5	0	0	5
Tandem walking	0	1	0	1	0	0	0	0
Finger-nose test	3	3	9	15	7	1	1	9
Diadochokinesia	5	3	10	18	9	1	1	11
Finger-thumb opposition	5	3	9	17	5	1	1	7
Mirror movements	1	2	6	9	2	0	0	2
Graphaesthesia	2	3	9	14	5	1	1	7
Stereognosis	4	3	9	16	6	1	1	8
Right/left orientation	5	3	10	18	9	1	1	11
Two point discrimination	1	0	1	2	0	0	0	0
Ozeretzki's test	5	3	10	18	8	1	1	10
Fist-edge-palm test	5	3	10	18	8	1	1	10
Arm holding test	2	3	7	12	4	1	1	6
Pronation-supination	4	3	10	17	8	1	1	10
Face-hand test	0	1	1	2	0	0	0	0
Speech and articulation	5	3	10	18	8	1	1	10

$\chi^2=4.872$, $df=15$, $P<0.9932$, NSS=Neurological soft signs, BPD=Brief psychotic disorder, SP=Schizophreniform psychosis, SC=Schizophrenia, df =Degree of freedom

Table 4 shows the distribution of the cases and total NSS scores as per severity of neurological impairment among the male and female gender groups. In our study, 10/19 male patients had moderate degree of impairment,

while surprisingly only 1/11 female cases were found to be moderately impairment. No patients from the either sex had severe impairment. From this table, it is obvious that severity of NSS were more in male in comparison to the female gender.

Table 3: Distribution of cases according to the severity of NSS in relation to age in years

Severity of NSS	Age						Total no. of cases
	15-24 (n=10)		25-34 (n=15)		35-50 (n=5)		
	No. of case	Total NSS score	No. of cases	Total NSS score	No. of cases	Total NSS score	
Mild (0-16)	6	59	9	118	4	47	19
Moderate (17-32)	4	81	6	118	1	18	11
Severe (33-48)	0	0	0	0	0	0	0

$\chi^2=16.289$, $df=2$, $P<0.0003$, NSS=Neurological soft signs, BPD=Brief psychotic disorder, SP=Schizophreniform psychosis, SC=Schizophrenia, df =Degree of freedom

Table 4: Distribution of cases according to the severity of NSS in relation to gender

Severity of NSS	Gender				Total no. of cases
	Male (n=19)		Female (n=11)		
	No. of cases	Total NSS score	No. of cases	Total NSS score	
Mild (0-16)	9	103	10	121	19
Moderate (17-32)	10	198	1	19	11
Severe (33-48)	0	0	0	0	0

$\chi^2=102.13$, $df=1$, $P<0.0001$, NSS=Neurological soft signs, df =Degree of freedom

The result of the statistical test is also found to be extremely significant.

Figure 4 shows the distribution of the cases according to the severity of NSS in relation to the male and female gender.

Structural relationship with NSS

In this study, we have attempted to find out whether the NSS abnormality in the different study groups is any way specific to any structure of the brain. We have divided the different types of NSS into different groups depending upon the functional relationship of the NSS with the different structure of the brain.

From Table 5, we find that in the brief psychotic disorder and schizophrenia categories, NSS score was highest in the cerebellum group, while in the schizophreniform psychosis category, it was highest in the parietal lobe. The results were not significant.

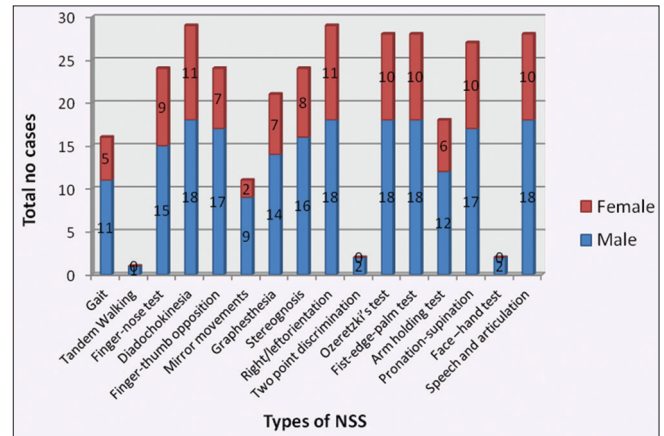
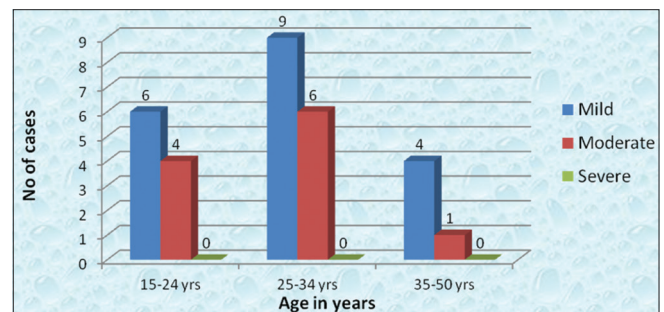
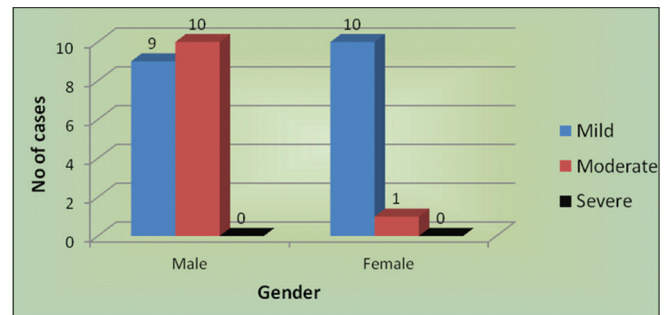
Figure 5 shows the distribution of total NSS score among the three groups of disorders under study in relationship to the different brain structures.

Discussion

Types of NSS in relation to age in years

In our study, maximum impairment was found in motor coordination among the three age groups, which ranged from 80-100%, followed by motor sequencing and sensory integrations. However, we have not found any remarkable change in pattern in the three different age groups and findings are also found to be statistically insignificant.

In a similar way, no significant association between age and types of NSS were reported by various studies,[2,24,25] and the findings of these studies support our study findings.

**Figure 2:** Types of NSS in relation to gender. NSS=Neurological soft signs.**Figure 3:** Distribution of cases according to the severity of NSS in relation to age in years. NSS=Neurological soft signs.**Figure 4:** Distribution of cases according to the severity of NSS in relation to gender. NSS=Neurological soft signs.

However, our study findings are contrasted by the findings of two studies, one by Tucker *et al.*[10] and the other by Manschreck and Ames,[26] who demonstrated sensory

Table 5: Structural relationship with NSS

Structures	BPD (n=14)		SP (n=4)		SC (n=12)	
	No. of patients	Total NSS score	No. of patients	Total NSS score	No. of patients	Total NSS score
Cerebellum						
Gait	8	8	3	3	5	5
Tandem walking	0	0	1	1	0	0
Finger-nose test	10	11	4	4	10	10
Diadochokinesia	14	18	4	6	11	16
Finger-thumb opposition	10	11	4	4	10	13
Mirror movements	3	3	2	2	6	6
Total score	51		20		50	
Parietal lobe						
Graphaesthesia	7	10	4	8	10	13
Stereognosis	10	11	4	8	10	12
Right/left orientation	14	23	4	8	11	17
Two-point discrimination	1	1	0	0	2	2
Total score	45		24		44	
Prefrontal lobe						
Ozeretzky's test	13	23	4	9	11	25
Fist-edge-palm test	13	22	4	9	11	18
Total score	45		18		43	
Mixed						
Arm holding test	6	6	4	4	8	8
Pronation-supination	12	16	4	5	11	14
Face-hand test	0	0	1	1	1	1
Speech-articulation	13	20	4	8	11	18
Total score	42		18		41	

$\chi^2=1.055$, $df=6$, $P=0.9835$. NSS=Neurological soft signs, BPD=Brief psychotic disorder, SP=Schizophreniform psychosis, SC=Schizophrenia, df =Degree of freedom

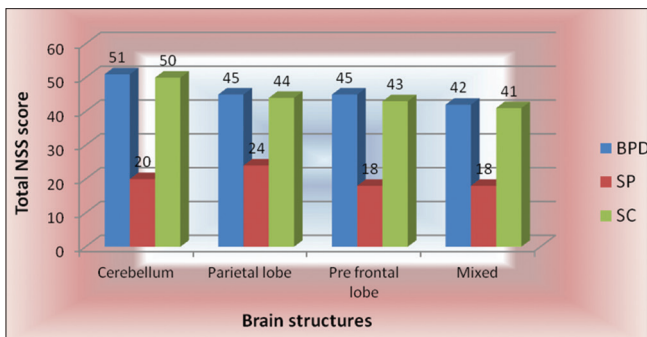


Figure 5: Structural relationship with NSS. NSS=Neurological soft signs, BPD=Brief psychotic disorder, SP=Schizophreniform psychosis, SC=Schizophrenia.

impairment to be significantly associated with age. Although none of these studies reported the exact percentages.

The difference in socio-demographic variables and the instrument used for detection of NSS may be the reason behind the difference in the observed results in the two studies.

Types of NSS in relation to gender

In our study, the impairment in motor coordination, sensory integration, and motor sequencing were found to be almost

equally distributed in both the male and female genders with a range from 89-100%. However, this association is found to be non-significant statistically.

The results of our study is consistent with the findings of few other studies who did not report any association between NSS and gender.[2,10,27,28]

However, there are some contrasting reports from different studies,[19,26,29,30] who have reported male predisposition towards increased neurological impairment.

Severity of NSS in relation to age in years

On comparing the severity of NSS with age, we have found the numbers of cases in all the three categories of ages are almost equally distributed and no predominance of particular type of NSS is found in any age group. However, the total NSS score is found to be significantly different in different age groups, i.e. 140 in the age group of 15-24 years, 236 in the age group of 25-34 years, and only 65 in the age group of 35-50 years. This association of total NSS score with the three different age groups on statistical analysis is found to be extremely significant.

Though we have searched various studies, we have not found any study which have commented on the association

between severity of NSS in the different age groups like that of us using the same measurement scale that we have used. We therefore cannot compare directly our findings on the severity of NSS with any other study.

Severity of NSS in relation to gender

On evaluating the severity with gender, we have found that in the male group, the numbers of cases having mild and moderate impairment are almost equal (9:10). But interestingly, in case of female, the ratio between mild and moderate group is 10:1. Statistical analysis also shows a highly significant association between severity of NSS and gender.

Although we have reviewed various studies, we cannot collect information from any past study that had evaluated the severity of NSS in relation to gender and hence, we are at present not been able to compare our results with any other study.

Structural relationship with NSS

Our study has made a novel effort to relate the different NSS functionally with different brain structures. The present study found that in the brief psychotic disorder and schizophrenia categories, the impairment in the cerebellar group of NSS was more, while in the schizophreniform category, the impairment is more pronounced in the parietal group of NSS.

Many previous studies have tried to evaluate the relationship of NSS with different brain structures and to corroborate them using various radio-imaging techniques, but no study could be found that have tested the functional relationship of NSS in different diagnostic categories and brain structures. Among these studies, Weinberger and Wyatt[11] reported the association of NSS and enlarged ventricular size, DeMyer *et al.*[31] reported a smaller right and left frontal areas, Schröder *et al.*[32] related motor coordination abnormalities with basal ganglia atrophy, and Dazzan *et al.*[33] and Thomann *et al.*[34] reported impairment in the motor and sensory coordination and integration with reduced grey and white matter densities in pre and post central gyri, premotor area, middle and inferior frontal gyri, cerebellum, caudate, and thalamus. Although the results of our study did not show significant association, the attempt to establish this relationship is unique in itself and it posits a greater significance when economic constraints becomes an issue.

However, large long-term studies are required to confirm the findings of our study which may in time shed a light on the association between the functional impairment in the various diagnostic categories with the different structure of brain, whereby any other means with the present technology we may not be able to detect any structural abnormality.

Limitations

1. Sample size was very small.
2. The findings of the study were not corroborated with radio- imaging techniques.

Conclusion

One interesting finding of our study was that when the association between the types of NSS with age and sex was evaluated using the number of patients in both groups, the results were not statistically significant. But, on comparing the total score of NSS among the three groups and both the male and female gender, the results turned out to be extremely significant with a trend indicating milder impairment in the female gender. We have made a novel attempt in our study to establish a functional relationship between the structural involvement and the three groups of disorders under study through the evaluation of NSS at the onset of symptoms, which at times may not be possible to diagnose through currently available radio-imaging techniques. We have definitely found a predominant involvement of the cerebellum in the brief psychotic disorder and schizophrenia groups, and the involvement of parietal lobe in the schizophreniform group, although the results were not statistically significant. We hope that in future larger studies with more number of patients will shed definite lights in the present study findings.

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