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ORIGINAL ARTICLE

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An exploratory study from eastern India on neurological soft signs and spontaneous movement disorders in schizophrenia spectrum disorders

Abstract

Background: Apart from the traditional symptoms of delusion and hallucination, soft signs of neurological dysfunction in psychotic disorder have the potential for addressing neurodevelopmental and neurodegenerative aetiology. **Aim**: The study explored the neurological soft signs (NSS) and spontaneous movement disorders (SMD) in the same patient population of schizophrenia spectrum disorders (SSD) and other psychotic disorders. **Materials and methods**: Patients were diagnosed with SSD and other psychotic disorders as per ICD-10 diagnostic criteria and were evaluated with the Heidelberg manual for NSS and Modified Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Rating Scale (SARS), and Barnes Akathisia Rating Scale (BARS) for assessing dyskinesia. **Results**: Total 16 patients with mean age of 28.7 (±7.7) years had a mean duration of 63.2 (±68.8) months' illness. Out 16 patients, 13 cooperated for assessment. Patients with schizophrenia had the mean Heidelberg score of 6.75 (±3.304). The scores of complex motor task, right/left spatial orientation, integrative functions, and hard signs varied but the motor coordination score was unwaveringly high in all the participants with SSD. Twenty per cent of SSD patients had dyskinesia. None had scored more than the upper limit of normal range in SARS. None of the participants had scored enough to qualify for akathisia. **Conclusion**: NSS and SMD emerge as distinct objective parameters for a group of psychotic disorder patients, especially SSD.

Keywords: Abnormal Involuntary Movement Scale. Motor Coordination. Dyskinesia. Psychotic Disorders.

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INTRODUCTION

The prevalence of schizophrenia is one per cent with usual onset during adolescence or early adulthood having a deteriorating course. It is a disabling psychiatric condition which impairs cognitive, emotional, and behavioural aspects of functioning.[1] The scientific interest in neurological abnormalities in schizophrenia dates to the time of Kraeplin and Bleuler, both of whom had noted neurological and behavioural abnormalities in the early life histories of adult schizophrenic patients. Bender (1947) even asserted that childhood schizophrenia was due to developmental encephalopathies in her monumental study on the condition.[2] Since then a number of literature supports structural anomaly in the brain of patients with schizophrenia[3] and abnormal finding in neurological evaluation.[4]

Approximately 60% of schizophrenic patients have been found to have abnormal neurological findings on evaluation referred to as "soft signs".[5] Neurological soft signs (NSS) are defined as "subtle neurological abnormalities comprising deficits in sensory integration, motor coordination, and sequencing of complex motor acts".[6] NSS are not always permanent and does not signify any localised pathology in brain but may represent complex brain function, and are probably because of disrupted neurodevelopment of the brain as a consequence of pre- or perinatal cerebral insult.[7] NSS have been consistently found in drug naive schizophrenia patients suggesting that NSS is an essential feature of the illness and not secondary to medication.[8] Neuroimaging studies revealed that NSS was associated with reduced grey or white matter densities in different parts of brain. This pattern of cerebral change associated with NSS support the model of 'cognitive dysmetria' involving disrupted cortico-cerebellar-thalamic-cortical circuit in schizophrenia.[9]

Abnormal involuntary movement in schizophrenia was believed to be because of medication. However, recent

findings suggest that dyskinesia may be one of the features of schizophrenia as many studies have found patients with schizophrenia who are not exposed to antipsychotics, yet have dyskinesia and parkinsonian signs.[10-12] Reports of abnormal involuntary movement date from the first description of the illness; long before the introduction of chlorpromazine in 1952, Kraeplin gave the description of the involuntary movement in patients with schizophrenia. He wrote:

"The spasmodic phenomena in the musculature of the face and of speech which often appear are extremely peculiar disorders. Some of them resemble movements of expression wrinkling of the forehead, distortion with the tongue… but besides we observe specially in the lip muscles, fine lighting-like or rhythmical twitching which in no way bear the stamp of voluntary movements…".[13]

Explanation of the abnormal movements in drug naive schizophrenics resembles the complex patterns of tics and mannerism rather than of those seen in classical tardive dyskinesia.[14] These spontaneous movements include making faces, myoclonic twitches on the face, grimaces, abnormal movement of the tongue, chewing, sucking, protruding tongue, jerking or tilting the head, rapid blinking of the eyelids, continuous squinting, fluttering eyelids, raising eyebrows, rhythmical or jerky movements of the limbs.[15] Their periodicity and uniform nature assist in distinguishing them from the non-uniform, irregular movements found in tardive dyskinesia.[16]

Pooled together, the presence of such obvious signs of neurological dysfunction such as NSS and spontaneous movement disorders (SMD) at various stages of disease inception and progression in schizophrenia spectrum disorders (SSD), may be ample proof of the neurodevelopmental/neurodegenerative aetiology of SSD and we aim to study the possible neurodevelopmental aetiology of SSD with the help of NSS and SMD.

Hypotheses

1. Most drug naive patients of SSD will have NSS.
2. Most drug naïve patients of SSD will have SMD.

Key questions

What is the prevalence of NSS and SMD in psychotic disorders and what is the possibility of neurodevelopmental or neurodegenerative aetiology?

MATERIALS AND METHODS

Participants' characteristics and study design

It was a cross-sectional observational study done in the Department of Psychiatry, Gauhati Medical College Hospital (GMCH), Guwahati during one year period between 2015 and 2016. Cases were defined as subjects having psychotic symptoms that were either defining factor or associated feature in their diagnosis according to the diagnostic criteria of ICD-10,[17] but have never been treated or never have received any form of psychotropic medications, at least in the preceding six months either as outdoor or indoor treatment, prior to the present visit. Sample subjects were taken from indoor, outdoor, and emergency patients, Department of Psychiatry, GMCH. Participants included in the study were of either sex, drug naïve as defined above, who were 15-50 years of age. Patients who were uncooperative, who had neurological disorder, head injury or who had a history of substance abuse were excluded. The study was approved by the institutional ethics committee of GMCH and written informed consent was taken from the participants.

Tools used for the assessments

a) Socio-demographic proforma standardised in the Department of Psychiatry, GMCH.
b) NSS was assessed by the Heidelberg manual[18] developed by Schroder *et al.*[19] The scale consists of total 16 items which evaluates the motor coordination (MOCO) (Ozeretski's test, speech articulation, diadochokinesia, pronation/supination, finger-to-thumb opposition); complex motor task (CMT) (finger to nose test, fist-edge-palm test); integrative functions (IF) (station and gait, tandem walking, two point discrimination); hard signs (HS) (arm holding, mirror movement); right/left and spatial orientation (RLSO) (right left orientation, face hand test, stereognosis, graphaesthesia). The internal reliability (Cronbach's α=0.85) and inter-rater reliability of 0.88 has already been established by Schroeder *et al.*[[19]
c) SMD was assessed by the Modified Abnormal Involuntary Movement Scale (AIMS).[20] This scale was developed in the 1970s by the National Institute of Mental Health (NIMH) for use in evaluating the presence and severity of choreoathetoid and other movements consistent with tardive dyskinesia. It consists of a formal part in which the patient is asked to perform a series of maneuvers and an informal part where he is observed without his knowledge that movement evaluation is being done. Dyskinetic movements in various body areas are observed and then rated as any one of zero (none), one (minimal), two (mild), three (moderate), or four (severe) for each area. The total score is then calculated and a score of at least two in two areas or a score of three in any area, signifies presence of dyskinesia.
d) Simpson-Angus Rating Scale (SARS) for rating extrapyramidal signs.[21] It assesses gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabellar tap, tremor, and salivation. Each item is rated in five point scale with zero standing for complete absence of the condition and four standing for presence of the condition in an extreme form. The score on the scale is calculated by adding the scores in each items and dividing by ten. Mean total score of 0.3 is taken as upper limit of normal range.
e) Barnes Akathisia Rating Scale (BARS) for assessing akathisia.[22] A global item score of greater than or equal to two was taken for labelling a participant positive for akathisia.
f) Modified BG Prasad's scale for classification was used to classify the socioeconomic status (Table 1).[23]

Table 1: Modified BG Prasad's scale for classification of socioeconomic status[23]

Social Class	Original classification of per capita income (Rs./month)	Revised classification for 2016 (Rs./month)
I (Upper Class)	100 and above	6261 and above
II (Upper Middle Class)	50-99	3099-6260
III (Middle Class)	30-49	1835-3098
IV (Lower Middle Class)	15-29	949-1834
V (Lower Class)	<15	<948

Statistical analysis

Descriptive analysis of the data was done. Categorical variables were shown as percentage and continuous variables as mean with standard deviation (SD).

RESULTS

Participants' characteristics

The total number of participants was 16 with mean age of 28.7 years with SD 7.7 years. There were equal numbers of male and female participants. The mean duration of illness was 63.2 months with SD 68.8 months. The socio-demographic detail of the participants is given in Table 2. 37.5% of the participants were diagnosed with schizophrenia and 12.5% diagnosed with schizoaffective disorder and equally 12.5% of the participants were diagnosed with schizophrenia with tic disorder. Frequency of participants with different psychiatric illness has been shown in Table 3. The mean duration of illness for participants with exclusive diagnosis of schizophrenia was 66 months with SD 81.25 months. Out of the 16 participants, three did not cooperate for assessment of NSS and dyskinesia.

NSS assessment findings

The mean Heidelberg score for schizophrenia was 6.75 with SD of 3.304. The mean Heidelberg score of the participants are shown in Table 4. The MOCO score for the participants in SSD was relatively stable when compared to score of CMT, RLSO, IF, and HS which varied in all the patients (Table 5).

Findings of SMD assessment

Assessment with AIMS revealed two out of 13 (15%) had dyskinesia. Both of them had the primary diagnosis of schizophrenia and one of them had comorbid tic disorder. The finding is shown in Table 6. However, if we only consider SSD (N=ten) then 20% had dyskinesia (N=two). Patients' dental status was normal and the informants had never noticed the movements while the patients were asleep.

Evaluation of the participants with SARS revealed none of them had mean total score more than 0.3 which is taken as the upper limit of normal range. None of the patients had akathisia when assessed with BARS. However, two patients with schizophrenia had nonspecific sense of inner restlessness.

Table 2: Socio-demographic data of the participants

Socio-demographic data	N	%
Sex		
Male	8	50
Female	8	50
Religion		
Hindu	11	69
Muslim	5	31
Occupation		
Unemployed	9	56.3
Homemaker	2	12.5
Teacher	2	12.5
Farmer	1	6.3
Business	1	6.3
Manager	1	6.3
Marital status		
Unmarried	8	50
Married	5	31.3
Separated	2	12.5
Widowed	1	6.3
Education		
Illiterate	3	18.8
Primary education	3	18.8
Secondary education	2	12.5
High school	2	12.5
Higher secondary	4	25
Graduate	2	12.5
Socioeconomic status		
Class I	2	12.5
Class II	6	37.5
Class III	6	37.5
Class IV	2	27.5

DISCUSSION

This paper presents the exploratory findings of NSS and SMD among population with psychotic disorders though the main population of interest was the one with SSD. We found that that MOCO score of all the participants with SSD was higher and similar when compared to the other scores in NSS assessment. Two out of ten participants with SSD had dyskinesia when assessed with AIMS. Assessment with SARS and BARS did not reveal any significant finding.

This study from the eastern part of India assessed both NSS and SMD in the same participants with SSD and other diagnosis. Earlier from this region, Bhandari

and Bhagabati[10] and Sharma and Nath[25,26] had explored SMD and NSS in patients with psychotic disorders respectively.

The mean age of the participants in this pilot study was 28.7 years which is similar to the studies done previously in first episode SSD from this region[10,24,25] as well as other parts of the world.[26,27] However, the age at the first psychiatric consultation depends on many factors like knowledge and attitude towards mental illness,[28] availability of mental health services, etc.

Table 3: Psychiatric diagnosis of the participants

Psychiatric diagnosis	N	%
Schizophrenia	6	37.5
Schizophrenia with tics	2	12.5
Schizoaffective disorder, manic type	2	12.5
Bipolar affective disorder	2	12.5
Severe depressive episode with psychotic symptoms	2	12.5
Mental retardation with psychosis	1	6.3
Unspecified nonorganic psychosis	1	6.3

Table 4: Mean Heidelberg score

Illness	Mean	N	SD
Schizophrenia	6.75	4	3.304
Schizophrenia with tics	9.50	2	4.950
Schizoaffective disorder, manic type	9.00	2	1.414
Bipolar affective disorder	3.00	2	1.414
Severe depressive episode with psychotic symptoms	4.50	2	4.950
Mental retardation with psychosis	26.00	1	-
Total	7.31	13	6.775

Our study showed presence of NSS in both schizophrenia and affective spectrum. This is in concordance with the study finding of Manschreck and Ames,[29] which found motor and sensory disturbance in 92% patients with schizophrenia and 52% patients with affective disorder, while the severity of the disturbance was found to be greater in the former group. Some other studies reported in lesser frequency which may be explained by the use of different tools and less stringent measures for assessment of NSS. MOCO score in our study showed similarity among the participants with SSD which suggest motor discoordination are more common in SSD and similar finding was observed in other studies.[25,26] Assessment with AIMS revealed two patients having dyskinesia. If Schooler and Kane's criteria[30] for spontaneous dyskinesia is considered, then only ten per cent (one in ten participants with SSD) can be labelled to have abnormal involuntary movement among SSD patients. According to the criteria, a score of two (mild) in at least two areas or a score of three (moderate) or four (severe) in one area is the requisite. This is slightly lower than that found by Bhandari and Bhagabati[10] which was 14%. This difference is because of very small sample size in the current study. The presence of dyskinesia is explained possibly by increased presynaptic dopamine and increased sensitivity in the nigrostriatal pathway.[31]

Chatterjee *et al.*[11] had found a prevalence of approximately 17% when assessed for extra pyramidal signs (EPS) and Koning *et al.*[31] found a prevalence of 38%. The differences in both the studies were because EPS was examined systematically with the use of SARS and with careful intake of only drug naïve cases in the Chatterjee *et al.*'s[11] group and less stringent rule for rating of EPS in the Koning *et al.*'s[31] group. Our study failed to find any parkinsonian features among the participants. However, the small sample size in our study does not let it qualify to comment on EPS in drug naïve SSD.

Table 5: Heidelberg score (mean)

Diagnosis	MOCO	IF	CMT	RLSO	HS	Mean Heidelberg score
Schizophrenia	6.25	0.25	0.00	0.25	0.00	6.75
Schizophrenia with tics	4.00	1.50	0.50	2.00	1.50	9.50
Schizoaffective disorder, manic type	4.00	0.00	2.50	1.50	1.00	9.00
Bipolar affective disorder	1.50	0.00	0.00	1.50	0.00	3.00
Severe depressive episode with psychotic symptoms	1.50	0.00	1.00	2.00	0.00	4.50
Mental retardation with psychosis	10.00	2.00	3.00	9.00	2.00	26.00

MOCO=motor coordination, IF=integrative functions, CMT=complex motor task, RLSO=right/left and spatial orientation, HS=hard signs

Table 6: Abnormal Involuntary Movement Scale score

Diagnosis	Facial and oral movements	Extremity movements	Trunk movements	Global judgement
Schizophrenia with tics	Minimal	None	Moderate	Severity, Overall: Moderate Incapacitance: Moderate Awareness: Aware, mild distress
Schizoaffective disorder, manic type	None	Minimal	None	Severity, Overall: Minimal Incapacitance: None Awareness: No awareness

Two of the participants with the diagnosis of schizophrenia reported nonspecific sense of inner restlessness, but none had qualified to be tagged as having akathisia. We did not find any literature related to akathisia in drug naïve psychotic disorder to compare our result.

Higher NSS score has been found to be associated with reduced gray matter at the precentral gyrus, the inferior frontal gyrus, the cerebellum, and the thalamus as well as was found to be associated with reduced white matter at the temporal lobe, the cerebellum, and the inferior frontal gyrus.[32] Smaller volume of thalamus has also been found to correlate with both the total score and motor subscale scores of NSS scale. As thalamus is known as the relay centre which screen and relay selected information between peripheral, cortical, and subcortical structures, the changes in this may possibly explain inefficiency in the communication between widespread brain region and result in abnormal behavioural expression of NSS.[32] The changes in different structures may suggest neurodegeneration, but the absence of gliosis poses a question on this hypothesis. It has been suggested that schizophrenia is the result of ongoing neurodevelopmental process and a neurodegenerative or neuroprogressive process [33]. The neuroprogressive process is developmentally determined decrease in the connections between cortical synapses.[34] NSS and SMD represent domains generally considered sharing neurobiological mechanisms of neurodevelopmental or neurodegenerative origin of schizophrenia and related psychiatric disorders, and exploring this may give answer to many unanswered questions related to the disorder. Though our study has its limitations like a small sample size, lack of any biological correlate, but we have tried assessing both NSS and SMD in the same group of participants.

Conclusion

As psychiatry is evolving and the diagnosis is moving towards more biological basis, NSS and SMD may be considered relevant points to be included in the diagnostic criteria provided the assessment is done in uniform by all.

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REFERENCES

1. Mueser TK, Jeste DV, editors. Clinical handbook of schizophrenia. New York: The Guilford Press; 2008.
2. Weinberger DR, Marenco S. Schizophrenia as a neurodevelopmental disorder. In: Hirsch SR, Weinberger DR, editors. Schizophrenia. 2nd ed. London: Blackwell; 2003:326-48.
3. Steen RG, Mull C, McLure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia. Br J Psychiatry. 2006;188:510-8.
4. Karp BI, Garvey M, Jacobsen LK, Frazier JA, Hamburger SD, Bedwell BS, *et al*. Abnormal neurologic maturation in adolescents with early-onset schizophrenia. Am J Psychiatry. 2001;158:118-22.
5. Trimble MR. The neurology of schizophrenia. Br Med Bull. 1987;43:587-98.
6. Heinrichs DW, Buchanan RW. Significance and meaning of neurological signs in schizophrenia. Am J Psychiatry. 1988;145:11-8.
7. Danielyan A, Nasrallah HA. Neurological disorders in schizophrenia. Psychiatr Clin N Am. 2009;32:719-57.
8. Browne S, Clarke M, Gervin M, Lane A, Waddington JL, Larkin C, *et al*. Determinants of neurological dysfunction in first episode schizophrenia. Psychol Med. 2000;30:1433-41.
9. Thomann PA, Wüstenberg T, Santos VD, Bachmann S, Essig M, Schröder J. Neurological soft signs and brain morphology in first-episode schizophrenia. Psychol Med. 2009;39:371-9.
10. Bhandari SS, Bhagabati D. Prevalence of spontaneous dyskinesia in first episode, drug naïve schizophrenia and its relation to the positive and negative symptoms of schizophrenia. Open J Psychiatry Allied Sci. 2017;8:113-23.
11. Chatterjee A, Chakos M, Koreen A, Geisler S, Sheitman B, Woerner M, *et al*. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. Am J Psychiatry. 1995;152:1724-9.
12. Puri BK, Barnes RE, Chapman MJ, Hutton SB, Joyce EM. Spontaneous dyskinesia in first episode schizophrenia. J Neurol Neurosurg Psychiatry. 1999;66:76-8.
13. Kirkpatrick B, Tek C. Schizophrenia: clinical feature and psychopathology concepts. In: Sadock BJ, Sadock VA, editors. Kaplan & Sadock's comprehensive textbook of psychiatry. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:1416-35.
14. Fahn S. The tardive dyskinesias. In: Matthews WB, Glaser GH, editors. Recent advances in clinical neurology. Edinburgh: Churchill Livingstone; 1984;4:229-60.
15. Fenton WS, Wyatt RJ, McGlashan TH. Risk factors for spontaneous dyskinesia in schizophrenia. Arch Gen Psychiatry. 1994;51:643-50.
16. Granacher RP Jr. Differential diagnosis of tardive dyskinesia: an overview. Am J Psychiatry. 1981;138:1288-97.
17. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
18. Pridmore S. Download of psychiatry [Internet]. University of Tasmania; 2006 [cited 2017 Aug 24]. Available from: http://eprints.utas.edu.au/287.
19. Schröder J, Niethammer R, Geider FJ, Reitz C, Binkert M, Jauss M, *et al*. Neurological soft signs in schizophrenia. Schizophr Res. 1991;6:25-30.
20. Guy WA. Abnormal Involuntary Movement Scale (AIMS). In: ECDEU assessment manual for psychopharmacology. Washington, DC: U.S. Department of Health Education and Welfare; 1976:534–7.
21. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212:11-9.
22. Barnes TR. A rating scale for drug-induces akhathisia. Br J Psychiatry. 1989;154:672-6.
23. Khairnar MR, Wadgave U, Shimpi PV. Updated BG Prasad socioeconomic classification for 2016. J Indian Assoc Public Health Dent. 2016;14:469-70.
24. Sharma P, Nath K. Neurological soft signs in psychoses. I: a comparative study of prevalence amongst drug naive first episode patients. Open J Psychiatry Allied Sci. 2016;7:15-22.
25. Sharma P, Nath K. Neurological soft signs in psychoses. II: an explorative study of structural involvement amongst drug naive first episode patients. Open J Psychiatry Allied Sci. 2016;7:23-30.
26. Hirjak D, Wolf RC, Koch SC, Mehl L, Kelbel JK, Kubera KM, *et al*. Neurological abnormalities in recent-onset schizophrenia and Asperger syndrome. Front Psychiatry. 2014;5:91.
27. Thomann PA, Wüstenberg T, Santos VD, Bachmann S, Essig M, Schröder J. Neurological soft signs and brain morphology in first-episode schizophrenia. Psychol Med. 2009;39:371-9.
28. Kumar D, Kumar P, Singh AR, Bhandari SS. Knowledge and attitude towards mental illness of key informants and general population: a comparative study. Dysphrenia. 2012;3:57-64.
29. Manschreck TC, Ames D. Neurologic features and psychopathology in schizophrenic disorders. Biol Psychiatry. 1984;19:703-19.
30. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry. 1982;39:486-7.

31. Koning JP, Tenback DE, Van Os J, Aleman A, Kahn RS, Van Harten PN. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. Schizophr Bull. 2010;36:723-31.
32. Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C, *et al*. Neurological soft signs are not "soft" in brain structure and functional networks: evidence from ALE meta-analysis. Schizophr Bull. 2014;40:626-41.
33. Lieberman JA. Pathophysiologic mechanisms in the pathogenesis and clinical course of schizophrenia. J Clin Psychiatry. 1999;60 Suppl 12:9-12.
34. McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry. 2000;57:637-48.

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