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First Episode Schizophrenia: Neurological Abnormalities and Prognosis

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Abstract

Background: Minor 'soft' neurological abnormalities in sensory and motor performance have been described in excess in people with established schizophrenia. But it remains to be seen whether they form a part of the vulnerability to this illness and improve with treatment. Prognosis in schizophrenia depends on multiple factors, especially the 'Duration of Untreated Illness' (DUI), which affects the type of initial presentation.
Objectives: The current study aimed at evaluating patients with first episode schizophrenia for their demographic profile, DUI, prevalence of neurological soft signs (NSS) and improvement with treatment and association between the DUI and NSS, and DUI and type of presentation.
Methods: This was a longitudinal follow-up study of 40 first episode schizophrenia patients attending the psychiatric OPD of a tertiary public hospital. Positive and Negative Syndrome Scale (PANSS) and Neurological Evaluation Scale (NES) were applied at predetermined intervals.
Results and Conclusions: The mean DUI was approximately 3 years. NSS were found in 83% of the sample with mean scores being 8.45 (baseline), 5.2 (6 months) and 3.3 (12 months), with significant improvement in the NES scores between baseline and 6 months ($p<0.001$) and 6 months and 12 months ($p<0.001$). Our study did not reveal any significant association between DUI and NES score at baseline and between DUI and type of presentation (German J Psychiatry 2013; 16(2): 75-80).

Keywords: first-episode schizophrenia (FES), neurological soft signs (NSS), duration of untreated illness (DUI)

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Introduction

Minor (soft) neurological abnormalities in sensory and motor performance have been described in excess in people with established schizophrenia. "Soft" neurological signs (SNS) or 'neurological soft signs' (NSS) are described as non-localizing neurological abnormalities that cannot be related to impairment of a specific brain region or are not believed to be part of a well-defined neurological syndrome. NSS are mild, presumably non-localizing, neurological impairments that are inferred from performance deficits in domains such as sensory integration, motor coordination, and motor sequencing. Preliminary evidence, from studies using relatively small samples suggests that higher total rates of NSS and motor problems are already present at the time of the first schizophrenia episode as well as both medicated and treatment-naïve individuals with schizophrenia (Dazzan & Murray, 2002; Venkatasubramanian et al., 2003). Rates of NSS are also elevated in individuals at high risk for schizophrenia compared to controls (Mittal et al., 2007). Soft signs have also been observed in other mental illnesses like OCD, but rates of NSS have been found to be more common and severe in schizophrenia (Jaafari et al., 2011). Original classical study by Heinrichs & Buchanan (1988) had shown that although soft signs are not specific to schizophrenia, they are found more often in patients with schizophrenia than in any other psychiatric disorders and healthy subjects. They also seem to be independent of medication status and neurological side effects (Kolakowska et al., 1985). Current views consider these signs as covariates of

attention (Mohr et al., 2003), verbal ability (Flashman et al., 1996) and visual-spatial memory (Sanders et al., 2004). It follows that NSS and cognitive findings have emerged as candidate endophenotypes for schizophrenia-spectrum disorders (Chan & Gottesman, 2008).

The prognosis in schizophrenia depends on multiple factors, especially the duration of untreated illness. 'Duration of untreated illness' (DUI) is the time interval between onset of psychotic symptoms and first effective treatment. Studies of first episode schizophrenia find that longer period of unchecked untreated illness is associated with a poorer prognosis and that long-term morbidity in some patients with schizophrenia may be prevented if patients are treated early with neuroleptics (Wyatt et al., 1997; Marshall et al., 2005; Thirthalli et al., 2011).

We undertook the study to evaluate the demographic variables, presence of NSS and the DUI in patients presenting with first episode schizophrenia in the Indian subcontinent.

Methods

This was a prospective follow-up study conducted in patients attending the psychiatry out-patient department of a tertiary hospital, after approval from the Institutional Ethics Committee**.** 105 patients of either sex and irrespective of age suffering from 'First Episode Schizophrenia (FES)', diagnosed as per ICD-10 (International Classification of Diseases) guidelines were enrolled in the study over a period of 6 months by systematic sampling technique (WHO, 1992). Patients were diagnosed as having FES by at least 2 experienced psychiatrists. Patients with a previously diagnosed psychiatric illness or any associated co-morbidity, e.g. substance abuse, mental retardation and organic disease were excluded. Only those patients who were drug naive and had no previous exposure to antipsychotics were included in the study. The final sample consisted of 40 patients who were then followed up for a period of 52 weeks after informed consent.

A proforma was prepared to study the various demographic variables and the DUI. Kuppuswamy's scale was used to assess the socio-economic status of the patients (Kumar et al., 2007). The DUI was operationalized as the time interval between the onset of psychotic symptoms and onset of treatment. A semi-structured interview following the model of Beiser et al. (1993) was conducted with the participant and carer to obtain information about the onset and development of symptoms and the early stages of treatment. Additional information was extracted from the participant's psychiatric records in order to verify dates about the onset of symptoms and treatment.

All patients were started on tablet risperidone (second generation antipsychotic) as it was freely available to the patients from the hospital and as it was also in accordance with Indian Psychiatric Society's Clinical Practice Guidelines for the management of schizophrenia for treatment initialization in first episode psychosis (Gautam & Avasthi, 2005). The average dose administered was 4–6 mg (200–300 chlorpromazine equivalents) along with tablets trihexyphenidyl and benzodiazepine for initial sedation which were then tapered in 4 weeks' time.

Patient's clinical symptoms were assessed using PANSS and neurological soft signs were assessed with NES. Both scales were applied by a single rater (author) to achieve minimal interrater variability. Extrapyramidal side effects were assessed clinically by authors and kept to the minimum using standard protocols to minimize confusion with NES tests.

Positive and negative syndrome scale (PANSS) (Kay et al., 1987). The PANSS is a scale used for measuring symptom reduction of patients with schizophrenia. The scale has 7 positive symptom items, 7 negative symptom items and 16 general psychopathology symptom items. Each item is scored on a 7-point severity scale.

Neurological evaluation scale (NES) (Buchanan & Heinrichs, 1989). The NES is a structured instrument for the assessment of neurological signs in schizophrenia. It comprises of 26 items designed to assess primarily three functional areas of interest - sensory integration, motor coordination and sequencing of complex motor acts, and others such as short-term memory, frontal release signs and eye movement abnormalities were also assessed. The total score was used in the study to quantify the severity of neurological impairment.

All the patients were followed up for a period of 52 weeks (1 year) from the time of enrolment in the study on a fortnightly basis to ensure proper compliance, monitoring and treatment. All medications were dispensed from the hospital dispensary. They were assessed using PANSS at baseline, 8 weeks, 24 weeks and 52 weeks. NES was applied at baseline, 24 weeks and 52 weeks. The total duration of the study was 18 months. There were no dropouts from the study.

Statistical Analysis

The data was analyzed using frequency distribution, ANCOVA and Pearson's correlation co-efficient with the SPSS version 17 for Windows.

Results

Population characteristics (Table 1). The mean age of patients was 35 ± 11.946 years. On assessing the prevalence of FES on the basis of gender in our sample, the male to female ratio was found to be 1.3:1. Majority of the patients (n=23, 58%) had no companion and were single or widowed. 92.5% (n=37) of the patients were Hindus. Almost 63% (n=25) of them were staying in nuclear family. We found an almost equal number of people from middle and lower class (as per Kuppuswamy's scale).

Table 1. Demographic details of patients (n=40)

Variables		
Age	Mean	35.5
	Standard deviation	11.9
Sex	Male	21 (52.5%)
	Female	19 (47.5%)
Marital status	Married	17 (42.5%)
	Single	23 (55%)
Religion	Hindu	37 (92.5%)
	Muslim	2 (5%)
	Christian	1 (2.5%)
Family type	Nuclear	25 (62.5%)
	Joint	13 (32.5%)
	Extended	2 (5%)
Socio-economic class	Upper	4 (0.1%)
	Upper middle	20 (50%)
	Lower middle	9 (22.5%)
	Lower	7 (17.5%)

Faith-healing practices. Our study found faith healing to be adopted by about 52.5% (n=21) of the families whereas 47.5% (n=19) of them did not visit any faith healers.

Duration of Untreated Illness (DUI). The DUI in our study was almost 3 years (mean: 35.9 months with S.D: 42.3 months) and the distribution was skewed due to the range being 1–144 months.

Prevalence and type of Neurological Soft Signs. On applying NES on first-episode neuroleptic-naïve schizophrenia patients, we found 33 (82.5%) patients having at least some NSS whereas 7 (17.50%) patients did not have any soft signs. Difficulty in complex motor acts was seen predominantly in Ozeretski (77.50%), fist-ring (67.50%) and fist-edge-palm (60%) tests whereas difficulty in sensory integration was seen in audio-visual integration (55%), right-left confusion (25%) and stereognosis (12.50%) tests. The least affected were 'frontal release signs' or primitive reflexes (glabellar, grasp, snout, suck) and eye movement coordination (convergence, gaze impersistence).

Improvement in Neurological Soft Signs on Follow-up (Table 3). On applying NES sequentially at baseline, we found a significant improvement in NSS over the follow-up period ($p<0.001$).

Association between duration of untreated illness, neurological soft signs and type of presentation (Tables 4.1 and 4.2)

On evaluating the association between 'DUI & NSS' and 'DUI & Positive and Negative symptoms' of schizophrenia as per PANSS at baseline, no significant association was found.

Table 2. Type of neurological soft signs

Category of signs	Soft signs	N	%
Sensory integration	A-V integration	22	55%
	Graphaesthesia	15	37.5%
	R-l confusion	10	25%
	Stereognosis	5	12.5%
	Extinction	5	12.5%
	Rhythm tap	15	37.5%
Motor coordination	Tandem walking	8	20%
	Rapid alternating movements	8	20%
	Finger thumb opposition	6	15%
	Finger-nose test	4	10%
Complex motor acts	Ozeretski	31	77.5%
	Fist ring test	27	67.5%
	Fist edge palm	24	60%
Primitive reflexes	Glabellar	11	27.5%
	Grasp	1	2.5%
	Snout	1	2.5%
	Suck	1	2.5%
Others	Memory	18	45%
	Tremors	10	25%
	Gaze impersistence	7	17.5%
	Romberg	4	10%
	Mirror movements	3	7.5%
	Synkinesis	3	7.5%
	Overflow	2	5%
	Convergence	2	5%

Discussion

The mean age of presentation in our study is in keeping with the general epidemiological findings that schizophrenia is more common in the age group of 15-30 years, with males having an earlier onset (Kaplan & Sadock, 2000).

The male-to-female ratio in our study (1.3:1) is in keeping with the other studies showing lower incidence in females (Thara et al., 1994; Aleman et al., 2003). A number of researchers have demonstrated that relationships in schizophrenic patients whether personal, familial or social were at a disadvantage, leading to difficulties in marrying or sustaining a relationship.

Majority of our patients were in nuclear family. Some researchers have found that living with a large family is crucial to the untreated status of the ill individual. The joint family system often credited with therapeutic qualities in providing care and protection to the patients resulting in better outcome, has its flip side; a large family with multiple caregivers and wage earners were able to compensate for the lack of contribution by the ill person and took care of them without any medical treatment as the burden and responsibility were shared. However, this contrasts with our finding of most patients staying in nuclear family but presenting late with DUI of almost 3 years.

Faith-healing practices are socially sanctioned in India and were found to be adopted by families irrespective of level of education or patient's/relative's belief in the cause of illness (Jiloha & Jugal, 1997). Thara et al. (1998) studied this high rate of visiting faith healers in India and found that spirits, witchcraft, and magic were considered to be responsible for possession states, hallucinations, irrelevant talk and bizarre behaviour which are the characteristic symptoms in schizophrenia.

Table 3. Improvement in Neurological Evaluation Scale Score on follow-up*

Variable		Mean	SD		Sum of Squares	df	Mean Square	F	P
Neurological Evaluation Scale Score	Baseline	8.5	7.1	Baseline–6 months	1237.2	16	77.3	24.9	<.001
	6 months	5.2	5.8						
	1 year	3.3	4.1	6–12 months	765	16	47.8	17.3	<.001

* ANCOVA
df, degrees of freedom

Our DUI of almost 3 years is in keeping with several studies where researchers have found DUI to be ranging from 5 – 120 months (Drake et al., 2000; Shrivastava et al., 2010). A number of factors like clinical, social, cultural, religious, economic and personal could determine the delay in the treatment of patients with first-episode psychosis. In a developing country like India where stigma is rampant, awareness is poor, accessibility of care is limited with use of faith healing and alternative forms of medicine being higher than seeking medical care, the DUI would be longer. Some researchers have hypothesized that a long DUI may have a negative impact on the long-term prognosis of these patients (Wyatt et al., 1997). Drake et al. (2000) found that personal characteristics such as attitudes towards health and illness would be critical in determining the duration before medical help is sought and this would also affect the attitudes towards medications.

On applying NES on first-episode neuroleptic-naïve schizophrenia patients, we found 33 (82.5%) patients having at least some NSS. Our findings of NSS in FES are supported by various studies where neuroleptic-naive first-episode patients had NSS before medication exposure. This is thought to be an intrinsic feature of schizophrenia as seen in some studies (Bachmann et al., 2005). Browne et al. (2000) and Cuesta et al. (1996) reported rates of NSS as high as 97.1% amongst neuroleptic-naïve subjects with psychosis and this was also reflected in our findings.

Our finding of more patients having deficits in complex motor tasks followed by sensory integration has been replicated by a few studies. Many have even tried to associate them to cognitive deficits. A study by Sewell et al. (2010) found that deficit in motor control is associated with lower intelligence, more cognitive deficits and deficit syndrome schizophrenia. On the other hand, deficit in sensory integration is associated with lower PANSS positive score and higher AIMS (Abnormal Involuntary Movement Scale) score. Eric Chen (1997) found that motor coordination signs were specifically related to impairments in prefrontal functions while sensory integration signs were associated with more generalized cognitive impairments in schizophrenia. Prevalence rates of 46% in fist edge palm test and 41% in rhythm tapping test have been observed in a study by Boks et al. (2000). They also found complex motor tasks and sensory integration to be more prevalent amongst schizophrenia patients than controls. But due to the dearth of studies on soft signs in mood disorders and other conditions, how far these findings are specific to the neuropathology of schizophrenia is hard to ascertain.

We found a significant improvement in NSS over the follow-up period, which has been replicated in several studies (Schröder et al., 1992). Improvement with medications suggests that NSS might be a consequence of dopaminergic activity. This notion accords with the difference in NSS between medication responders and non-responders (Madsen et al., 1999). The significant improvement may also suggest that the NSS could be a state-characteristic rather than a trait-characteristic of schizophrenia. Comparing the soft signs with healthy controls may help further to differentiate the same.

Several studies did not find any association between the DUI and symptom profile at presentation in keeping with our finding (Barnes et al., 2000; Üçok et al., 2004). Harrigan et al. (2003) and Malla et al. (2004) found a relation between DUI and negative symptoms at presentation which is contrary to our finding. Several other researchers also failed to find this association (Schmitz et al., 2007). One possible explanation for the failure to observe such a relationship at first episode is that for most people in the sample the presentation to psychiatric services is likely to have been prompted by reaching a threshold level of severity of symptoms, thus obscuring any relationship with DUI.

The theory of long term process activity in chronic cases leading to acquired, irreversible deficits may not be true in all cases, as we did not find any significant association between DUI and NSS. This is in contrast to studies which have found persistent elevation of neurological soft sign scores in chronic cases thereby hinting at a still enduring process activity reflecting premorbid changes of neurodevelopmental origin or the presence of acquired, irreversible deficits (Weinberger, 1999).

Limitations

- There was a selection bias in recruitment of the cases as the sample belonged to a tertiary care centre and did

Table 4.1. Association between Duration of Untreated Illness with PANSS

Variable		Mean	SD	r	p
DUI		35.9	42.3		
Symptom profile at baseline	Positive	19.3	6.1	-0.04	0.8
	Negative	18.6	7.8	-0.05	0.7
	GPS	31.7	8.6	0.07	0.6

r, Pearson's correlation efficient

Table 4.2. Association between Duration of Untreated Illness with NSS

Variable	Mean	SD	r	p
DUI	35.9	42.3		
Baseline NSS	8.4	7.1	0.19	0.2
NSS at one year	3.3	4.1	-0.02	0.8

r, Pearson's correlation efficient

not reflect the prevalence in the general population.

- Neuroleptic medication was not strictly standardized amongst the patients.
- Extrapyramidal side effects were evaluated clinically. Standardized scales were not applied.
- Rater had received no formal training in applying PANSS and NES.
- Comparability amongst studies on NSS in schizophrenia is limited because of the absence of a universally accepted structured instrument.
- Results were not compared with healthy controls.

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