Original Article

Neurocognitive Deficits in Remitted Cases of Schizophrenia: a tertiary hospital based cross-sectional study

Sayantan Chattopadhyay[1], Kaustav Chakraborty[2], Pinaki Sarkar[3]

[1]1st year Post-Graduate Trainee, Department of Psychiatry, College of Medicine and JNM Hospital, WBUHS, Kalyani, Nadia, West Bengal, Pin -741235, Email– sayant0244@gmail.com

[2]Professor and Head, Department of Psychiatry, College of Medicine and JNM Hospital, WBUHS, Kalyani, Nadia, West Bengal, Pin -741235, Email – drkaustav2003@yahoo.co.in

[3]Assistant Professor, Department of Psychiatry, College of Medicine and JNM Hospital, WBUHS, Kalyani, Nadia, West Bengal, Pin -741235, Email – pinakisarkar@gmail.com

Corresponding author

Kaustav Chakraborty,Professor and Head, Department of Psychiatry, College of Medicine and JNM Hospital, WBUHS, Kalyani, Nadia, West Bengal, Pin -741235, **Email:** drkaustav2003@yahoo.co.in

ABSTRACT

Background: Cognitive deficits are one of the core symptoms of schizophrenia that evolve during the disease process. The cognitive domains mostly impaired are executive functions, memory, fluency, processing speed, working memory, attention, and delayed recall.

Aims and Objectives: In index study, authors included seventy remitted patients with schizophrenia (rated on PAN-SS scale) and assessed with Addenbrooke's Cognitive Examination – version III (ACE III), and Montreal Cognitive Assessment Test (MoCA).

Result:
The majority of the subjects in index study had schizophrenia of a mild degree as assessed by PAN-SS scale; mean positive symptom score was higher than the mean negative symptoms score. Overall, the most commonly reported symptoms were delusion (positive), passive social withdrawal & lack of spontaneity (negative) & unusual thought content (general psychopathological) in the study. On ACE III, more than four-fifth (82.9%) of the subjects showed abnormal deficits and severely compromised cognitive functions. Attention, language, and total ACE-III scores did not show difference across gender, but memory score was found to be higher in males (13.58 ± 5.22) compared to females (12.51 ± 3.53). Females had higher fluency rates (8.2968.29 ± 1.83) & visuospatial abilities (12.18 ± 3.31) compared to males. On MoCA, the language domain was the most affected. Majority of the samples had mild impairment (51.4%) in cognitive function.

Conclusion: Majority of The remitted patients with schizophrenia had cognitive deficits in multiple domains which is likely due to the disease process itself.

Keywords: Schizophrenia, Remitted patients, Neurocognitive deficits

Introduction

Schizophrenia is one of the most complex, chronic & challenging of all psychiatric disorders that affect how a person thinks, feels, and behaves. The prevalence of schizophrenia is approximately 3 per 1000 population in India where 1.1 billion people reside and approximately 24 million people or 1 in 300 people (0.32%) in the world.[1-2] Schizophrenia most commonly has its onset in late adolescence or early adulthood. It rarely occurs before adolescence & after the age of 40 years & onset tends to happen earlier among men than women. Schizophrenia is characterized by positive symptoms (delusion, hallucination, disorganized speech & thinking, catatonia), negative symptoms (flat affect, alogia, avolition, anhedonia, sociality), affective symptoms and neurocognitive symptoms (impairment of working memory, executive functions, verbal fluency, attention & disturbances in selection & processing of information).Recent evidence shows that 50-70% of patients with schizophrenia have neurocognitive deficits and that can be explained by the glutamate hypothesis. Cognitive dysfunction in schizophrenia has been identified in most cognitive domains, basic sensory and perceptual functions, and higher-order cognitive, including selective & sustained attention, working memory, episodic memory, processing speed & problem-solving. Recent evidence suggests that a variant in dysbindin which slightly elevates the risk for schizophrenia is associated with the severity of negative symptoms & generalized cognitive deficits.[3]

Schizophrenia has always been considered an illness with life-long disability. The studies on outcome of schizophrenia have shown significant betterment with the advent of antipsychotics. The trend of outcomes over 100 years, from the late 19th century to the late 20th century is such that, the number of individuals with schizophrenia having good outcomes, has increased from 30% to 37%.[4]

Earlier, it was thought that the overall improvement was largely based on clinical symptomatology. But, over the last few decades, cognitive functioning has been established as a predictor of quality of life and social/ occupational functioning, especially in the areas of the ability to sustain employment and problem solving skills that are necessary for daily living activities. Thus, the emphasis is currently on improving the quality of life, to improve the overall outcome of the illness. Over the years, the interest of researchers in neurocognition has seen many ups and downs. Since the birth of the 21st century, this particular domain of schizophrenia has been studied intensely.[5]

A remitted patient with schizophrenia has been defined by the Remission in Schizophrenia Working Group (RSWG) (2005) to set specific Operational criteria for the assessment. The criteria consist of two elements: A symptoms-based criterion: - They correspond to Eight items in PAN-SS and this item score should be < 3 to classify them as remitted. The items are delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms, blunted affect, social withdrawal & lack of spontaneity. A time-based criterion requires remission to be persistent for a minimum of six months.[4]

This study focuses on neurocognitive deficits and executive functioning difficulties in remitted schizophrenia patients in a tertiary care hospital of the eastern part of India.

Aims and Objectives

- To find out the prevalence of Neuro-cognitive deficits in remitted patients of schizophrenia.

Methodology

a) **Study type:** Observational cross-sectional study

b) **Inclusion / Exclusion criteria:**

Inclusion criteria:

I. Patients with schizophrenia diagnosed as per ICD-10 classification of mental & behavioural disorders by 2 independent psychiatrists and fulfilling the Remission in Schizophrenia Working Group criteria (RSWG, 2005) for remission.

II. Both gender

III. Age – 18 to 50 years

IV. Able to read and write English, Hindi and Bengali

V. Patients providing written and informed consent.

Exclusion criteria:

I. Patients having a history of dementia, stroke, intracranial operative procedure, autism, intellectual disability, and major neurological disorders e.g. Parkinson's disease, Huntington's disease and so on and so forth

II. Patients having a history of diabetes and hypertension for more than 10 years

III. Patients having comorbid psychiatric disorders as per Mini International Neuropsychiatric Interview (MINI)

IV. Age less than 18 years and more than 50 years

c) **Study population**: All consecutive patients diagnosed with schizophrenia as per ICD-10 and fulfilling "Remission" criteria as per RSWG, 2005 who will be attending the outpatient department of Psychiatry of COMJNMH, Kalyani between October 2022 to October 2023 and satisfying the inclusion and exclusion criteria as enumerated above. The remission criteria of schizophrenia as per RSWG, 2005 criteria go as follows - A remitted patient of Schizophrenia is defined by "Remission in Schizophrenia Working Group (RSWG) (2005) Criteria".[6] The criteria consist of two elements: A symptoms-based criteria which correspond to eight items in PAN-SS and these item scores should be< 3 to classify them as remitted. The items are delusions, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms, blunted affect, social withdrawal and lack of spontaneity, and a time-based criterion that requires remission to be persistent for a minimum of six months[7].

d) **Sample size/design**: All consecutive patients with schizophrenia attending the Psychiatry outpatient department within a 12-month study period and satisfying the inclusion & exclusion criteria. From the review of the literature, it was found that the prevalence of neurocognitive deficits in schizophrenia ranged from 13% to 34%. The median of this range was 23.5%. Therefore, the expected P became 0.23. With a precision (d) of 0.1 and 95% level of confidence the sample size came out to be 69 (using a sample size calculator).[8] Therefore, a sample of 70 subjects was taken.

e) Study Instruments

- Sociodemographic and clinical proforma
- Positive and negative syndrome in schizophrenia (PANSS) scale
- Mini International Neuropsychiatric Interview (MINI)
- Addenbrooke's Cognitive Examination-III (ACE III)
- Montreal Cognitive Assessment Test (MoCA).
- Informed consent form in all 3 languages- Bengali, English & Hindi.

f) Data collection and interpretation:

Patients with a clinical diagnosis of Schizophrenia as per the ICD-10 classification of mental and behavioral disorders confirmed by two independent psychiatrists, attending the outpatient department of Psychiatry of COMJNMH, Kalyani between October 2022 to October 2023 and meeting the inclusion and exclusion criteria (after applying PAN-SS to ascertain which patients would meet the RSWG, 2005 criteria) were approached for participation in the study. They were explained about the nature of the research and patients who agreed to participate and provided informed consent were recruited. A cross-sectional examination was completed over one session (one hour and thirty minutes). The MINI was administered to rule out other psychiatric disorders. The sociodemographic and clinical proformas were filled in. After that, these patients were assessed using ACE-III & MoCA.

g) Statistical analysis:

The statistical software SPSS version 22 was used for the analysis. Descriptive analysis was computed in terms of mean and standard deviation with range for continuous variables and frequency with percentage for ordinal and nominal variables. Correlations between the variables were assessed using Pearson's product-moment and Spearman's rank-order correlation. Any p-value ≤ 0.05 will be taken as statistically significant.

h) Ethical clearance:

Ethical clearance from the Institutional Ethics Committee (IEC) of the College of Medicine and JNM Hospital, WBUHS, Kalyani was sought and obtained.

Results

The mean age of the sample was 32.62 years. Majority of the sample was comprised of Hindu (81.4%), male (61.4%), subjects from rural (70%) background, belonging to joint families (54.3%). About half of the subjects were unmarried (51.4%) and majority studied up to intermediate (27.1%). Majority of the subjects were unemployed (54.3%) followed by shop owners and farmers (18.6%) with an income of < Rs.10,000 per month (78.6%).

The mean age at the time of first diagnosis was 27.20 years while the mean duration of illness at the time of assessment was 7.45 years. Subjects had a mean body weight of 58.08 kgs. Majority of the subjects did not have any medical comorbidities e.g. diabetes mellitus (94.3%) and hypertension (84.3%). Majority of the subjects did not have a family history of Schizophrenia (70%) & Bipolar affective disorder or Depression (88.6%). About two-thirds (77.1%) of the subjects were taking medications for more than seventy-five percent of days in the last three months. Haloperidol (8.6%) is the only first-generation anti-psychotic drug that had been given to subjects while majority of the subjects received Olanzapine (67.2%) and Risperidone (61.5%) as second-generation antipsychotics.

When rated by PAN-SS, delusions (98.6%) were the most common positive symptom followed by conceptual disorganization (88.6%). Hallucinatory behaviour was present in almost two-third of the subjects (70%). Passive social withdrawal & lack of spontaneity were the most common (80%) negative symptoms, whereas blunted affect (61.4%) & poor rapport (58.6%) was present in nearly two-third of the subjects. Unusual thought content was present in almost three-fourths (82.9%) of the subjects. Anxiety (61.4%) and mannerism & posturing (68.6%) were present in two-third of the subjects.

Table 1 shows the PAN-SS score of the subjects and gender-wise break up. In index study, males (15.16 ± 2.48) had a higher mean PAN-SS positive score compared to females (14.03 ± 1.28) but no such difference was seen in the case of total negative scores.

Table-1 PAN-SS score of the subjects (N=70)

PAN-SS Scores	Gender	Mean± S.D.
Total PAN-SS Positive score	Male	15.16 ± 2.48
	Female	14.03 ± 1.28
Total PAN-SS Negative score	Male	13.51 ± 2.763
	Female	13.00 ± 2.61
Total PAN-SS General Psychopathology score	Male	30.23 ± 5.76
	Female	31.22 ± 5.24
Total PAN-SS Score	Male	58.90 ± 8.26
	Female	58.25 ± 6.59

Addenbrooke's cognitive examination assesses five domains of cognitive functions - attention, memory, fluency, language & visuospatial abilities. The frequency distribution of ACE – III individual domains is listed in Table 2. Attention, language, and total ACE-III scores did not show difference across gender, but memory score was found to be higher in males (13.58 ± 5.22) compared to females (12.51 ± 3.53). Females had higher fluency rates (8.2968.29 ± 1.83) & visuospatial abilities (12.18 ± 3.31) compared to males.

Table-2 Score distribution of various ACE-III domains and their gender-wise break up (N=70)

ACE Category	Gender	Mean ± S.D.
ACE Attention	Male	13.30 ± 3.73
	Female	13.07 ± 3.01

ACE Category	Gender	Mean ± S.D.
ACE Memory	Male	13.58 ± 5.22
	Female	12.51 ± 3.53
ACE Fluency	Male	7.74 ± 2.49
	Female	8.29 ± 1.83
ACE Language	Male	19.53 ± 4.44
	Female	19.88 ± 4.88
ACE Visuospatial	Male	11.60 ± 4.26
	Female	12.18 ± 3.31
ACE Total Score	Male	65.86 ± 18.24
	Female	65.96 ± 12.96

More than four-fifth (82.9%) of the subjects showed abnormal deficits and severely compromised cognitive functions while only a small percentage (5.7%) of subjects showed normal cognitive functions.

MoCA is a sensitive tool for cognitive impairment assessing multiple domains of neurocognition like visuospatial abilities, naming, attention, language, abstraction, delayed recall, orientation. The total mean MoCA score was 17.68 ± 6.09 and the least score was obtained in the language domain (0.65 ± 0.81). Majority of the samples had mild impairment (51.4%) in cognitive function.

Table-3. Descriptive statistics and frequency distribution of MoCA

MoCA Domains	MEAN ±S.D.	N (%)
MoCA Visuospatial	2.95 ± 1.55	
MoCA Naming	2.55 ± 0.75	
MoCA Attention	3.50 ± 1.88	
MoCA Language	0.65 ± 0.81	
MoCA Abstraction	1.10 ± 0.68	
MoCA Delayed Recall	1.21 ± 1.24	
MoCA Orientation	5.17 ± 1.28	
MoCA total Score	17.68 ± 6.09	
MoCA Categories		
Normal (>25)		5 (7.1%)
Mild Impairment (18-25)		36 (51.4%)
Moderate Impairment (10-17)		20 (28.6%)
Severe Impairment (<10)		9 (12.9%)

Discussion

The sociodemographic profile of the subjects included in index study did not differ on most of the variables from patients excluded from the study. This suggests that the study population was representative of patients with remitted schizophrenia. The study group consisted of subjects of either gender in their mid-thirties. However, males outnumbered females. The excess of male patients of remitted schizophrenia in their mid-thirties in current study is similar to typical finding of the epidemiology of schizophrenia described in literature[1,2,6]. A previous gender-based study on patients with schizophrenia from the southern part of India has also reported similar age distribution[1]. Our finding of male preponderance is in keeping with most of the studies, which reported an excess of male subjects.[1,3,6] The majority of the subjects came from rural backgrounds and most of them studied up to intermediate which is typical of the population attending the psychiatry outpatient facility at the hospitals of West Bengal as reported in earlier studies.[9,10] Majority of the subjects in the index study were unemployed & had family income of less than Rs. 10,000 per month which is similar to previous studies done in India.[9] Unemployment could be due to stigma at workplace, presence of positive symptoms, and cognitive deficits.

The age of onset of illness was in the mid-twenties while the mean duration of illness was around seven years at the time of intake into the study. The findings related to age of onset in index study is similar to the typical profile of Schizophrenia described in the literature.[9,11]

The longer mean duration of illness in index study was probably due to the skewed data with a wide range. Thirty percent of the subjects had a family history of schizophrenia & only 11% of subjects had a family history of affective illness. This is similar to the earlier finding of lower rates of family history reported in patients with remitted schizophrenia in previous studies.[9]

In the index study, among positive symptoms, delusions (98.6%) were the most commonly reported symptoms followed by conceptual disorganization (88.6%). Hallucinatory behaviour, although a hallmark of Schizophrenia, was present in over two-third of the subjects (70%). Passive social withdrawal & lack of spontaneity (80%) were the most common negative symptoms, while blunted affect (61.4%) & poor rapport (58.6%) was present in two-third of the subjects. This finding corroborated with the findings from previous studies.[12] Unusual thought content was present in almost three-fourths (82.9%) of the subjects. Anxiety (61.4%) and mannerism & posturing (68.6%) were present in two-third of the subjects. The mean PAN-SS positive score is higher than the mean negative score in index study. However, most of the studies on neurocognitive deficits in schizophrenia had higher mean PAN-SS negative scores in contrast to index study.[6]

Index study showed impairment across all the five cognitive domains as assessed by ACE III. Maximum dysfunction was observed in the fluency domain followed by the memory domain while language domain was relatively preserved. Similar pattern was noted in previous study also.[13] In the MATRICS Consensus Cognitive Battery, the fluency test was used as an indicator of the speed of processing.[14] A study by Beilen et al. observed that in patients with schizophrenia, verbal fluency was predicted by psychomotor speed but not by memory or executive functioning.[15] A Meta-analyses by Mesholam and Schaefer et al. observed that the domain of processing speed also showed high dysfunction along with memory.[16,17] The meta-analysis by McCleery found that patients with first-episode schizophrenia exhibited marked impairment in the speed of processing.[17] The study by Shakeel et al. on Indian patients with chronic schizophrenia using a computer-based paced semantic verbal fluency test showed that patients with schizophrenia scored significantly inferior to healthy controls.[18] In index study, the fluency domain showed significant dysfunction similar to the above studies.

A review by Radanovic observed that in comparative studies of language impairment in schizophrenia and aphasia, both the groups performed similarly on tasks of language comprehension, naming, and repetition with the presence of abundant semantic paraphasias.[19] A meta-analysis by Mesholam et al. of studies assessing language dysfunction showed a moderately large effect size of −0.88 with individual test effect sizes ranging from (−1.2) to (−0.67).[16] It also showed that studies involving a higher percentage of first-episode schizophrenia patients taking antipsychotic medication showed smaller effect sizes. A meta-analysis by Schaefer et al. showed an effect size of −0.68 for verbal ability.[20] In this study, language was observed to be relatively unimpaired, compared to other domains.

Limitations

The following limitations must be kept in mind while interpreting the results of this study - the time-bound nature of the study dictated a small sample size and only a limited period of evaluation. The sample consisted of 70 consecutive outpatients attending a tertiary care general hospital psychiatric unit. Results cannot thus be generalized to other patient populations. The ACE-III scale has lower sensitivity; therefore, it may not pick up mild cognitive decline, while MOCA has higher sensitivity & lower specificity compared to ACE-III, but its score needs to be adjusted for age & education, making it complex.

Conclusion

The majority of the subjects in index study had Schizophrenia of a mild degree as assessed by PAN-SS scale, mean positive symptom score was higher than the mean negative symptoms score in the PAN-SS scale. Overall, the most reported symptoms were delusion (positive), passive social withdrawal & lack of spontaneity (negative) & unusual thought content (general psychopathological) in the study. On ACE III, MORE than four-fifth (82.9%) of the subjects showed abnormal deficits and severely compromised cognitive functions. All the cognitive domains were affected. Attention, language, and total ACE-III scores did not show difference across gender, but memory score was found to be higher in males compared to females (12.51). Females had higher fluency rates & visuospatial abilities compared to males. On MoCA, the language domain was the most affected. Majority of the samples had mild impairment (51.4%) in cognitive function. Therefore, it can be safely concluded that, remitted patients with schizophrenia have deficits in different cognitive domains which is most likely due to the disease process itself.

Funding: This research received no external funding.

Conflict of interest: Nil

References

1. Loganathan S, Murthy RS. Living with schizophrenia in India: gender perspectives. Transcultural psychiatry. 2011; 48 :569-84.

2. Mental health systems in selected low- and middle-income countries: a WHO-AIMS cross-national analysis. WHO: Geneva, 2009

3. Mosiołek A, Gierus J, Koweszko T, Szulc A. Cognitive impairment in schizophrenia across age groups: a case-control study. BMC psychiatry. 2016 ;16 :37.

4. Okasha TA, Hussein H, Shorub E, Nagi H, Moustafa AA, El-Serafi D. Cognitive dysfunction among inpatients and outpatients with schizophrenia: relationship to positive and negative symptoms. Middle East Current Psychiatry. 2020 ; 27 :1-7.

5. Dehelean L, Romosan AM, Bucatos BO, Papava I, Balint R, Bortun AM, et.al. Social and Neurocognitive Deficits in Remitted Patients with Schizophrenia, Schizoaffective and Bipolar Disorder. Healthcare 2021; 9: 365.

6. Raveendranathan D, Joseph J, Machado T, Mysore A. Neurocognitive and clinical correlates of insight in schizophrenia. Indian Journal of Psychiatry. 2020 ;62:131.

7. Lambert M, Karow A, Leucht S, Schimmelmann BG, Naber D. Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later. Dialogues in clinical neuroscience. 2010;12;393-407.

8. Naing, L., Winn, T. and Rusli, B.N. Practical Issues in Calculating the Sample Size for Prevalence Studies. Medical Statistics. Archives of Orofacial Sciences 2006;1: 9-14.

9. Solanki RK, Kumar A, Satija Y, Gupta S, Singh P. An Indian experience of neurocognitive endophenotypic markers in unaffected first-degree relatives of schizophrenia patients. Indian Journal of Psychiatry. 2016;58: 20.

10. Chattopadhyay S, Patil NM, Nayak RB, Chate SS, Singh OP. Neurocognitive profile in Indian individuals genetically at risk of schizophrenia. Indian Journal of Psychological Medicine 2020;42:155-61.

11. Caldiroli A, Serati M, Orsenigo G, Caletti E, Buoli M. Age at onset and social cognitive impairment in clinically stabilized patients with schizophrenia: an ecological cross-sectional study. Iranian Journal of Psychiatry 2018 ;13:84.

12. Bora E, Binnur Akdede B, Alptekin K. Neurocognitive impairment in deficit and non-deficit schizophrenia: a meta-analysis. Psychological Medicine. 2017;47:2401-2413. doi:10.1017/S0033291717000952

13. Bhat PS, Raj J, Chatterjee K, Srivastava K. Cognitive dysfunction in first-episode schizophrenia and its correlation with negative symptoms and insight. Ind Psychiatry J. 2021 ;30:310-315. doi: 10.4103/ipj.ipj_107_20. Epub 2021) Oct 28. PMID: 35017817; PMCID: PMC8709515.

14. Kern RS, Green MF, Nuechterlein KH, Deng BH. NIMH-MATRICS survey on assessment of neurocognition in schizophrenia. Schizophr Res. 2004 ;72:11-9. doi:10.1016/j.schres.2004.09.004. PMID: 15531403.

15. van Beilen M, Pijnenborg M, van Zomeren EH, van den Bosch RJ, Withaar FK, Bouma A. What is measured by verbal fluency tests in schizophrenia? Schizophr Res. 2004;69:267-76. doi: 10.1016/j.schres.2003.09.007. PMID: 15469198.

16. Mesholam-Gately RI, Giuliano AJ, Golf KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. Schizophrenia Research 2010 ;117: 327.

17. McCleery A, Ventura J, Kern AS, et al. Cognitive functioning in first-episode schizophrenia: MATRICS Consensus Cognitive Battery (MCCB) Profile of Impairment. Schizophrenia Research. 2014; 157: 33-39.
18. Shakeel MK, Halahalli HN, Kumar K, Jain S, John JP. Utility of a computerized, paced semantic verbal fluency paradigm in differentiating schizophrenia and healthy subjects. Asian J Psychiatr. 2014 ;7:22-7. doi: 10.1016/j.ajp.2013.09.010. Epub 2013 Sep 30. PMID: 24524705.
19. Radanovic M, Sousa RT, Valiengo L, Gattaz WF, Forlenza OV. Formal Thought Disorder and language impairment in schizophrenia. Arq Neuropsiquiatr. 2013; 71: 55-60. doi: 10.1590/s0004-282x2012005000015. Epub 2012 Dec 18. PMID: 23249974.
20. Schaefer J, Giangrande E, Weinberger DR, Dickinson D. The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophrenia research. 2013; 150: 42-50.