Cognitive deficits in familial schizophrenia

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Background: Cognitive impairment is a core feature of schizophrenia and has been observed in subjects with and without a family history of schizophrenia. Nonetheless, there is a paucity of research directly contrasting cognitive profiles in schizophrenia patients and normal people where family history is present and those where the family history is absent. Aim: This study aimed to compare cognitive functions in patients with schizophrenia who had a family history with those that did not and healthy controls. Materials and Methods: Fifty consecutive schizophrenia patients were assessed on admission and follow-up after 6 months of treatment using a specially prepared pro forma, the Positive and Negative Syndrome Scale, and the PGI Battery of brain dysfunction is the name given to the test. An equal number of age- and sex-matched normal control subjects were also assessed. Results: Visual memory scores in this study show improvement between baseline and follow-up in schizophrenia patients with/without a family history. Both verbal learning and memory increase between baseline and follow-up but do not reach control levels. Reasoning and problem-solving deficits follow a similar pattern and are causative in the inability to adapt to a changing world. Speed of processing shows improvement with treatment. Working memory deficits in patients improve with treatment. Conclusions: In this study, all six cognitive domain scores in schizophrenia improved after 6 months of treatment but did not reach the control population level. Individuals with the highest cognitive deficits in the scales were the ones who had a family history of schizophrenia.

Keywords: Cognitive deficits, familial schizophrenia, PGI battery of brain dysfunction, Positive and Negative Syndrome Scale, verbal memory, visual memory, working memory

The French psychiatrist (1809–1873) Benedict Morel first used “De’mence pre’oce” to describe deteriorated patients whose illness began in adolescence. Emil Kraepelin (1856–1926) translated Morel’s “de’mence pre’oce” to “dementia precox” to emphasize the change in cognition (dementia) and early onset (precox).[1] Aside from giving schizophrenia its name, Bleuler understood at an intuitive level that cognitive impairment was a core part of the illness.[2] He made an important distinction between two types of symptoms: fundamental and accessory. Fundamental symptoms are essentially cognitive in nature. Bleuler made many conceptual contributions, but perhaps, most relevant to this discussion is his view that psychotic symptoms were secondary to fundamental symptoms, including attentional problems. Research on the cognitive impairment of schizophrenia went forward, and its major features were reliably described: (i) all domains of cognition, including attention, executive function, secondary (storage) memory, working memory, and semantic memory may be affected; (ii) the pattern of deficits may vary widely among individuals with schizophrenia; (iii) the mean deficit in these domains may be 1–3 standard deviations below normal,[3–5] although about 15% of patients with schizophrenia test within the normal range in all domains;[6] (iv) for most patients, impairment is only slowly progressive after the first episode of psychosis;[7,8] and (v) some components of the deficit are present during childhood and early adolescence but usually in mild form.[7,9] This led to the conclusions

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that widespread decline in cognition occurs during the prodromal period (before the onset of psychosis), the first psychotic episode, or both and that prevention of the evolution of the cognitive deficit during these two periods might be of great value, if possible.\[10\]

Cognitive deficits are clearly central to the illness and meet several critical criteria for being considered as important “endophenotypes.”\[11\] They are stable, present in attenuated forming relatives, presumed to be genetically simpler than the illness phenotype, and measured with high reliability. Although schizophrenia is a heritable condition, linkage studies in which diagnosis is used as a phenotype have been disappointing, as few significant or replicable chromosomal loci have been identified.\[12\] Using psychiatric diagnosis as the major phenotype may be a major confound. One possible reason is that people may not inherit schizophrenia per se but rather a variety of information-processing deficits from which schizophrenia emerges. In other words, although impairment in any given cognitive process may extract only a small cost in social and vocational functioning, a constellation of impairments may be disabling and result in the emergence of psychosis. Thus, understanding the genetic architecture of individual processes may well be critical for understanding the genetics of schizophrenia. There is a paucity of research directly contrasting cognitive profiles in schizophrenia patients and normal people where family history is present and those where the family history is absent. In view of the paucity of Indian studies, the present work was undertaken to evaluate cognitive deficits in schizophrenia patients with and without a family history.

**MATERIALS AND METHODS**

This prospective, longitudinal study was conducted during the period July 2013 to September 2015 at a tertiary care hospital attached to a medical college. The proposal for the study was submitted to the institutional ethical committee and ethical clearance was obtained before starting the study. All the subjects included in the study gave written informed consent.

**Sample**

Fifty consecutive schizophrenia patients diagnosed as per the International Classification of Diseases (ICD) 10 Diagnostic Criteria for Research\[13\] admitted in a tertiary care hospital with neuropsychiatric facility were compared with 50 normal age- and sex-matched subjects (who were not on any known treatment or substance abuse) after their written consent. In addition, the following criteria were fulfilled before the patients were taken for the study.

**Inclusion criteria for patients**

Patients with schizophrenia diagnosed as per ICD 10 criteria were taken into the study irrespective of age and sex. Patients were drug naïve or drug free, defined as a period of 4 weeks for all psychotropics and anti-Parkinsonism drugs. Drug-free for depot antipsychotics was 8 weeks.

**Exclusion criteria for patients**

1. All other cases of psychotic disorders
2. Those with a history of head injury, seizures, metabolic disorders, history of substance abuse, those on antipsychotic medication, and history having had electroconvulsive therapy (ECT) in the past
3. Intellectually disabled patients
4. Patients with chronic renal failure and those on dialysis or other organic disorders with behavioral/psychotic features.

**Inclusion criteria for control subjects**

Subjects were matched for age and sex with schizophrenia patients included in the study.

**Exclusion criteria for control subjects**

1. Those with a history of any psychiatric diagnoses
2. Those with a history of head injury, seizures, metabolic disorders, history of substance abuse, those on psychotropic medication, and history having had ECT in the past
3. Those with intellectual disability
4. Patients with chronic renal failure and those on dialysis or other organic disorders with behavioral/psychotic features.

**Tools used in the study**

**Sociodemographic pro forma**

This self-made pro forma included questions about demographic and clinical details and detailed family history of psychotic illness spanning three generations to detect genetic vulnerability as per the protocol.

**Positive and Negative Syndrome Scale**

The Positive and Negative Syndrome Scale (PANSS) is used for measuring symptom severity of patients with schizophrenia. The name refers to the two types of symptoms in schizophrenia: positive symptoms, e.g. hallucinations and delusions, and negative symptoms. The PANSS had alpha coefficients of 0.73 and 0.83.\[14\]

**PGI memory scale**

The PGI Memory Scale was constructed and standardized in the Indian population. This scale contains 10 subtests: (1) remote memory (personal information), (2) recent memory (current information), (3) mental balance (3 items of time related), (4) attention and concentration (forward
and backward), (5) delayed recall (5 words), (6) immediate recall (3 sentences), (7) retention for similar pairs (5 pair of words), (8) retention for dissimilar pairs (5 pair of words), (9) visual retention (5 cards), and (10) recognition (10 pictures).

**METHODS**

Complete details of the patient were recorded on the sociodemographic pro forma. All the patients with schizophrenia were also screened on the PANSS. They were also evaluated by the PGI Memory Scale while admitted in the hospital and at follow-up after treatment for 6 months.

**Statistical analysis**

The data were statistically analyzed using SPSS (IBM, Chicago, IL, USA). Following statistical tests were used in the study to analyze the data: Pearson's Chi-square test, Mann–Whitney test, and Spearman's correlation coefficient. $P < 0.05$ was taken as statistically significant.

**RESULTS**

Demographic characteristics and family history in study and control subjects are shown in Table 1. Out of 50 cases in the study group, 13 had a family history of mental illness compared to none in the control group. This is a statistically significant finding. From Table 2, it is evident that the scores of working memory, verbal memory, vigilance + attention, reasoning and problem solving, visual memory, and speed of processing (SOP) between the cases and controls where family history is present and the follow-up cases are statistically significant. It is evident that the scores of working memory, verbal memory, vigilance + attention, reasoning and problem solving, visual memory, and SOP between the cases where family history is present and the control group are statistically significant. The scores of working memory, verbal memory, vigilance + attention, reasoning and problem solving, visual memory, and SOP between the cases where family history is present and the control group are statistically significant, whereas it is not statistically significant in Reasoning and problem solving (RPS) and visual memory scores where family history is present and the control group [Table 3]. From Table 4, it is evident that the scores of working memory, verbal memory, vigilance + attention, reasoning and problem solving, visual memory, and SOP between the cases where family history is absent and the follow-up group are statistically significant. It is also evident that the scores of working memory, verbal memory, vigilance + attention, reasoning and problem solving, visual memory, and SOP between the cases where family history is absent and the control group are statistically significant. The average score for follow-up between cases where family history is absent in all the

| Parameter                                      | Study ($n=50$) | Control ($n=50$) | T-test/$\chi^2$ | $P$     |
|-----------------------------------------------|---------------|-----------------|----------------|--------|
| Age (years), mean (SD)                        | 35.76 (12.504)| 34.22 (11.758) | 0.63           | $>0.05$ (NS) |
| Sex                                           |               |                 |                |        |
| Male                                          | 27            | 30              | 0.367          | 0.545 (NS) |
| Female                                        | 23            | 20              |                |        |
| Religion                                      |               |                 |                |        |
| Hindu                                         | 48            | 46              | 1.04           | 0.593 (NS) |
| Muslim                                        | 1             | 3               |                |        |
| Christian                                     | 1             | 1               |                |        |
| Education                                     |               |                 |                |        |
| Illiterate                                    | 1             | 0               | Fishers        | 0.464 (NS) |
| Up to 10 standard                             | 34            | 31              |                |        |
| Above 10 standard                             | 15            | 19              |                |        |
| Occupation                                    |               |                 |                |        |
| Housewife                                     | 19            | 17              | Fishers        | 0.0015 |
| Employed                                      | 22            | 33              |                |        |
| Unemployed                                    | 9             | 0               |                |        |
| Marital status                                |               |                 |                |        |
| Married                                       | 31            | 32              | 0.04           | 0.835 (NS) |
| Unmarried                                     | 19            | 18              |                |        |
| Family history of mental illness              |               |                 |                |        |
| First generation                              | 1             | 0               | Fishers        | 0.001 |
| Second generation                             | 6             | 0               |                |        |
| Third generation                              | 6             | 0               |                |        |
| No                                            | 37            | 50              |                |        |

SD – Standard deviation; NS – Not significant
domains is less than that of the controls and is statistically significant except in the domain reasoning and problem solving which is statistically not significant [Table 4].

**DISCUSSION**

Historically, cognitive symptoms were considered the primary manifestations of schizophrenia. However, there was a growing sense of urgency in medicine toward the relatively easily treatable symptoms such as hallucinations and delusions when effective antipsychotics became available those reduced the symptoms. This also led to a decline in interest in research into the cognitive aspect of schizophrenia. In recent times, however, there is growing recognition of the role of cognition in early diagnosis, pathology, and treatment response. In this study, an attempt is made to find the relationship between six domains of cognition and various manifestations of schizophrenia through the use of relevant instruments such as PGI Memory Scale and PANSS. Toward this end, 50 patients with schizophrenia and 50 normal subjects as controls were evaluated. There were no differences in age, education status, religion, and marital status. They are comparable and that the results of the study are likely to be valid for this reason.

There was a significant difference in employment status with nine schizophrenia patients being unemployed. Sustaining the employment status when the person suffers from a disorder such as schizophrenia is not easy, especially when
cognitive domains are affected. A study by McGurk and Meltzer showed that patients maintaining full-time employment were significantly better educated and engaged in work tasks that were more cognitively complex than patients who were employed part-time or unemployed. This possibly suggests that both premorbid function and cognitive abilities affect employment status. Furthermore, employment has been shown to be an important element of treatment outcome, positively associated with symptomatic remission and recovery. Research from the large-scale CATIE study found that environmental and demographic variables were associated with employment outcomes. The present study too finds that those who were employed were able to achieve remission faster than those unemployed.

Table 1 shows that there was no family history of schizophrenia in the control group. There was a history of schizophrenia in one patient in first, six in second, and six in third generation relatives of test subjects. A majority of test subjects (n = 37) had no family history. The risk of development of schizophrenia in siblings with schizophrenia is likely in 7%–10% dizygotic twins, 10%–17% monozygotic twins, 40%–50% if both parents are schizophrenics, and >50% second-degree relatives 2%–6% risk of developing schizophrenia as against a general population risk of 1%.

Table 2 shows there is an increase in the cognitive performance of patients in all six domains which is a statistically significant rise in all patients’ scores between baseline and follow-up in patients with a family history of schizophrenia. While previous studies have shown relatively lower impairment in visual memory as compared to other domains of cognition, this study shows a significant difference between visual memory scores in study cases with presence of family history and the controls. There was however no significant difference between follow-up cases and controls in visual memory. These findings are significant in view of the fact that visual memory does have a correlation with employment retention and successful rehabilitation. Therefore, any improvement in the visual memory on treatment would yield some benefit.

Table 2 also shows a statistically significant difference between the patients with a family history of schizophrenia and the control population in all six domains. Vigilance and attention deficits have been shown to make even simple activities such as reading and watching TV very difficult for schizophrenia patients. Verbal learning and memory deficits are shown to be large and functionally significant for patients. The learning component is affected more than memory. In this study, there is a significant deficit in verbal learning and memory that improves on treatment but does not reach the level of the control group.

Reasoning and problem-solving measures show a significant decrease in cases with improvement on treatment but do not reach the normal (control group). The reasoning and problem-solving deficit has previously been correlated with the inability of patients to adapt to rapidly changing external circumstances. The SOP measures in this study show a slowing in schizophrenia patients that improve during the follow-up, i.e., after treatment. SOP has been shown to correlate with activities of daily living, functioning, job tenure, and independent life. Slower responses to social cues may hamper social relationships in patients.

Working memory deficits too followed a similar pattern in the course of this study. This is to be expected as research has shown working memory (WM) to be closely related to other cognitive impairments in schizophrenics and with functional outcomes among treated patients. Table 2 also demonstrates that there is an improvement in the 6six domains between first examination of the patients and at the time of follow-up.

Table 3 shows a statistically significant difference between the patients with a family history of schizophrenia and the control population in all the domains. This effect is present even at follow-up where the scores show an increase in the domains. Table 4 shows that there is a significant difference between the six domain scores of the test subjects without family history and the control group.

Table 4 also shows a significant difference between the test subjects at follow-up who do not have a family history of schizophrenia and control subjects except for the RPS domain where there is no statistically significant difference at follow-up between the test and the control. This would indicate that reasoning and problem solving in follow-up patients without family history has increased to the level of the controls, whereas this has not happened in the other five domains where the improvement [as shown in Tables 2 and 3] has not brought the patients to the level of control subjects.

Limitations
Different drug regimens were used for different patients over the course of their treatment. Some were treated with multiple antipsychotics, some were treated with single antipsychotics, whereas others were treated with different classes of antipsychotics, i.e. typical versus atypical antipsychotics. The antipsychotics themselves have an effect on the cognitive profile of the patient. The difference between the different drug regimens among the patients and the drugs having an effect on the cognition of patients are two very significant confounding factors that can have an effect on the outcome of this study. The
sample size of 50 patients who were admitted in the tertiary hospital for treatment of schizophrenia might be too less to substantiate and generalize the findings for identification and follow-up of the cognitive deficits of schizophrenic patients.

**CONCLUSIONS**

In this study, all six cognitive domain scores in schizophrenia improved after 6 months of treatment but did not reach the control population level. Individuals with the highest cognitive deficits in the scales were the ones who had a family history of schizophrenia.

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**Conflicts of interest**

There are no conflicts of interest.

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