ORIGINAL ARTICLE

Association of Frontal Lobe Abnormalities with the Severity of Schizophrenia

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ABSTRACT

Schizophrenia is a severe and chronic mental disorder causing a loss of touch with reality with cognitive impairment being a core aspect. Multiple studies hypothesize that these underlying structural and functional frontal changes are the primary reason for both the cognitive deficits. A cross-sectional study was done at Teerthanker Mahaveer Medical College and Research Centre, UP, India, on 30 patients having schizophrenia along withand 30 age-matched control to determine the association between the severity of schizophrenia and objective structural and functional abnormalities of the frontal lobe. All enrolled participants (both cases and controls) underwent a detailed history taking and clinical examination. The assessment protocol was based on three objective, complementary modalities – a severity scale named 'positive and negative syndrome scale' (PANSS), a structural neuroimaging measure (CT scan), and a functional cognitive battery (FAB). Statistically significant differences were observed in greater 'positive and negative syndrome scale' (PANSS) score in cases ($p<0.05$) and classifying them as "Markedly Ill". The frontal assessment battery (FAB) also showed statistically significant differences between the case and control groups across all major outcome parameters. The critical correlation analyses confirmed strong, significant relationships in the patient group with PANSS score versus structural distance as well as functional versus structural distance. Our study demonstrated both a significant anatomical abnormality and a profound functional deficit in patients. The positive correlation between the PANSS score and the objective CT distance confirms the degree of structural deterioration in the frontal-callosal axis.

Keywords: Frontal lobe abnormalities, corpus callosum, schizophrenia, positive and negative syndrome scale, frontal assessment battery

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INTRODUCTION

Schizophrenia is recognized globally as a severe and chronic mental disorder, which affects an individual's behaviour, thinking, and emotions. This often causes a loss of touch with reality. The aetiology is still unknown though it is believed to be associated with genetic, neurochemical (dopamine, glutamate), and environmental factors (prenatal infections, substance abuse).[1]

Diagnosis historically relies on the identification

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of clinical signs and symptoms characteristic of psychosis. The symptoms are usually classified as: Psychotic positive symptoms (including hallucinations, delusions, and thought disorders), Negative symptoms (characterized by a loss of motivation, reduced social interaction, difficulty expressing emotions), and Cognitive symptoms (poor concentration and attention, memory loss).[1,2]

This classification highlights the complexity and disabling nature of the disorder, which leads to life-long outcomes. The chronic and destructive nature of the disorder calls for comprehensive patient management instead of one based solely on observed symptoms. In order to ensure early and precise diagnosis, prognosis charting and therapeutic interventions, it is critical to find objective and quantifiable diagnostic criteria to support the existing the subjective, qualitative assessment models we possess now. The significance of this research lies in its potential to introduce quantifiable neurobiological markers which are directly linked to the clinical signs of deterioration in schizophrenia.[1,3]

Among the various manifestations of schizophrenia, cognitive impairment is a core aspect. It is arguably the most debilitating feature and is often a predictor of poor functional outcome or prognosis in contrast to a case with only positive psychotic symptoms.[1]

This presents with patients/attendants frequently complaining of trouble in complex problem-solving and reduced analytical thinking. These are hallmark functions of the frontal lobe. Impairments in the control processes required for goal-oriented behaviour are regarded as the most characteristic neuropsychological symptoms of schizophrenia.[2] The degree of these cognitive impairments can be closely intertwined with the stability of negative symptoms.[1]

The observation of cognitive impairment is a strong and consistent indicator of frontal lobe impairment in clinical presentation suggestive of frontal lobe pathologies which may be anatomical or biochemical.[3]

Multiple studies hypothesize that these underlying structural and functional frontal changes are the primary reason for both the cognitive deficits and the severe psychotic manifestations seen in affected individuals.[4]

Investigations using advanced imaging techniques have provided substantial evidence confirming that frontal lobe malfunctioning is a feature of schizophrenia. Studies using Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans have documented measurable structural and functional deviations in participants suffering from schizophrenia as compared to normal healthy volunteers.[5]

The following tools are considered as core assessments in schizophrenia cases:

For clinical assessment, the PANSS (Positive and Negative Syndrome Scale) is used to find the severity of positive, negative, and general symptoms. This measurement places the patient on the spectrum of illness severity.[6]

For structural assessment, CT scans are performed on all participants which measures the distance from the frontal pole to the anterior-most point of the corpus callosum. This metric is an objective test of structural frontal abnormalities.[7]

Another is for functional assessment; the Frontal Assessment Battery (FAB) is used to objectively quantify functional deficits which directly test for functional impairment related to frontal lobe anomalies.[8]

The primary aim of this study is to determine the association of frontal lobe abnormalities with the severity of disease in patients diagnosed with schizophrenia.

The novelty of the study is a combination of three complementary assessment modalities: the PANSS for clinical severity of schizophrenia, CT scans to assess for structural integrity, and the Frontal Assessment Battery (FAB) to check for functional capacity, within a single cross-sectional design. This multimodal approach facilitates in the formation of a bridge between the clinical symptoms and underlying structural and functional brain abnormalities.[9,10]

Previous literature confirms the presence of a relationship between neuropsychological, structural, and functional frontal abnormalities with the severity of schizophrenia (assessed by PANSS), even though the exact relationship is still undetermined and unproven.[11] Closing this gap requires a study that directly links quantitative clinical tests to objective structural and functional investigations.

There exists a significant lack of data for the Indian subcontinent concerning schizophrenia and its relation to frontal abnormalities, both

structural and functional. Neurobiological parameters, like measurements pertaining to the frontal lobe can exhibit variation depending on population. Therefore, it is necessary to have findings that rule out this bias so as to make the findings applicable within the Indian healthcare system.[12] In lieu of these shortcomings, this study was outlined to determine the relationship between neuropsychological, structural and functional frontal abnormalities with the severity of schizophrenia in a tertiary care hospital in Uttar Pradesh region of India.

METHODS

This cross-sectional study was done on participants visiting our tertiary care hospital and is an **e**pidemiological study, enrolling equal number of age matched cases and control visiting the Psychiatry Department of our tertiary care hospital after taking a written informed consent. A total of 60 participants were enrolled in the study. The cases enrolled in the study were patients diagnosed with schizophrenia visiting both inpatient and outpatient departments of psychiatry of the hospital after they gave a written informed consent. The age-matched healthy controls were recruited from the local population during field and hospital visits. A total of 30 patients diagnosed with schizophrenia and equal number of age-matched healthy controls were enrolled in the study. All participants who were more than 18 years of age of either gender and were willing, proficient and compliant to all clinical and participatory requirements of the study were included in the study. All patients diagnosed with schizophrenia by the Consultant Psychiatrists were enrolled as cases and age-matched participants during field and hospital visits as controls were included in the study.

Any patients suffering from any other mental disorder, undergoing electroconvulsive therapy, under the influence of any substance abuse or under de-addiction program and patients diagnosed with schizophrenia visiting the emergency department were excluded from the study. Any participant with any other clinically significant or uncontrolled concomitant medical disease that the investigator believed could impact the ability to participate or influence the study results were also excluded from the study.

Procedure: All enrolled participants (cases and controls) underwent a detailed history taking and clinical examination after taking their written informed consent. The assessment protocol was based on three objective, complementary modalities: a clinical severity scale (PANSS), a structural neuroimaging measure (CT scan), and a functional cognitive battery (FAB).

Outcomes: Assessment of Clinical Severity using the PANSS (Positive and Negative Syndrome Scale) was utilized to quantify the severity of schizophrenia.[13] It is a 30-question, structured instrument which is used to rate and evaluate a multidimensional spectrum of symptoms which include positive, negative, depressive, and neuromotor dimensions with a score range from 1 (absent) to 7 (extreme). This rating was the used to classify the severity of the illness according to the clinical global impression (CGI) severity with the following score ranges for mildly ill (score range from 58 to74), moderately ill (score range from 75 to 94), markedly ill (score range from 95 to 115) and severely ill when the score range was more than 116.[13]

Assessment of functional abnormalities was done with Frontal Assessment Battery (FAB), by assessing the functional capacity and cognitive functioning of the frontal lobe, providing the functional correlate of the disease. The battery consists of six subtests. Similarity testing was used to assess for abstract reasoning as the patient finds the common factor among a number of given objects. Lexical testing was used to assess mental flexibility/cognitive search where the patient was asked to tell words starting with the same letter (excluding proper nouns). Motor programming was tested using Motor Series Testing in which the patient observed and repeated a task done by the person assessing. Conflicting Instruction Trial tested for interference testing by making the patient perform 2-3 tasks when given specific yet opposing tasks. Sustained control was tested by go-no-go test and patient was instructed to act on one stimulus and withhold action on another. Prehension behaviour test analysed for primitive grasp reflex that is, if the patient grasps the examiner's hand despite instruction not to, it suggests frontal lobe functional impairment.[14]

For assessment of structural abnormalities, all participants underwent standard computed tomography (CT) scans of the head to evaluate the structural integrity of the frontal lobe. The

key structural manifestation measured was the distance from the frontal pole to the anterior-most point of the corpus callosum. This specific measurement is considered an easy-to-perform index of structural frontal abnormalities. The mean distance in a healthy individual is 5.4±0.57 cm.[15]

The collected data was stored in excel sheet, where the necessary cleaning was done before exported to SPSS. IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA) was used for final analysis. Quantitative data was summarized and tabulated as mean±standard deviation (SD). Statistical analysis was performed using a combination of parametric (two-tailed Student's t-test) and non-parametric tests (Chi-Square test), along with Pearson correlation coefficient test, to determine the association between the three primary variables (PANSS score, CT distance, and FAB score). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 60 participants were recruited in the study, 30 participants as control and 30 patients who were suffering from Schizophrenia. Table 1 shows the characteristics of patients suffering from schizophrenia and age-matched controls. Both groups were comparable with the following characteristics showing no differences: the mean age, sex, marital status, level of education, and occupation (p>0.05). However, the participants differed significantly in terms of socioeconomic status (p<0.05). Moreover, there was a statistically significant difference in the PANSS, cognitive function test and the distance between corpus callosum and frontal pole (mm) between the cases and controls (p<0.05). Table 2 shows the comparison of frontal battery assessment amongst both groups. There was a statistically significant difference in all the parameters between the groups (p<0.05), which included motor series, similarities, lexical fluency, go/no-go, conflicting instructions, and prehension behaviour. Table 3 shows correlation of distance between corpus callosum and frontal pole with PANSS and frontal battery assessment in cases of schizophrenia. Positive correlations were observed in distance between corpus callosum and frontal pole with PANSS and all parameters of FAB (p<0.05).

Table 1: Comparison of cases versus control (N=60)

Variables	Case (n=30)	Control (n=30)	p-value
Age (in years) (Mean±SD)	26.67±5.04	28.13±5.58	>0.05*
Sex (Male:Female)	9:21	16:14	>0.05*
Marital Status (Married:Unmarried)	20:10	13:17	>0.05*
Education level Uneducated Up to Class 5 Up to Class 8 Up to Class 10 Up to Class 12 Graduate and above	 8 1 4 2 9 6	 8 1 3 1 10 7	>0.05*
Occupation House Wife Employed Unemployed	 12 12 6	 7 14 9	>0.05*
Urban: Rural Setup	25:5	22:8	>0.05*
Socioeconomic Status Middle-Class Lower Middle-Class Upper Middle-Class	 18 11 1	 7 13 10	<0.05*
Accompanied by Spouse Siblings Parents	 12 12 6	 10 11 9	>0.05*
Age of onset of illness (in years) (Mean±SD)	24.43±4.22	---	
PANSS Score (Mean±SD)	91.50±23.29	35.57±4.09	<0.05#
Cognitive Function Test (Mean±SD)	9.77±3.42	17.47±0.78	<0.05#
Distance between corpus callosum and frontal pole (mm) (Mean±SD)	49.29±2.34	53.15±1.03	<0.05#

#=Student's t-test was applied, *=Chi-square test was applied.

Table 2: Frontal Assessment Battery in cases and controls (N=60)

Variables	Case (n=30) (Mean±SD)	Control (n=30) (Mean±SD)	p-value
Similarity testing	1.20±0.72	2.83±0.46	<0.05
Lexical fluency	1.27±0.69	2.67±0.48	<0.05
Motor series testing	1.93±0.64	3	<0.05
Conflicting instruction trial	1.83±0.70	3	<0.05
Go-no-go test	1.60±0.86	3	<0.05
Prehension behaviour	1.97±0.62	3	<0.05
Total	9.77±3.42	17.47±0.78	<0.05

Student's t-test was applied.

Table 3: Correlation of distance between corpus collosum and frontal pole with PANSS and FAB in cases of schizophrenia (n=30)

Variables	r	p-value
Positive and Negative Syndrome Scale (PANSS)	+0.95	<0.05
Similarity testing	+0.79	<0.05
Lexical fluency	+0.50	<0.05
Motor series testing	+0.49	<0.05
Conflicting instruction trial	+0.68	<0.05
Go-no-go test	+0.79	<0.05
Prehension behaviour	+0.67	<0.05
Total score of frontal assessment battery	+0.93	<0.05

Pearson correlation coefficient test was applied.

DISCUSSION

This cross-sectional study was done to assess that increased disease severity in schizophrenia is inversely associated with the structural integrity and functional performance of the frontal lobe. The study found a statistically significant reduction in the mean distance between corpus callosum and frontal pole in cases as (49.29±2.34 mm) compared to controls (53.15±1.03 mm) ($p<0.05$). Similarly, the patient with schizophrenia had a statistically significantly lower FAB score (9.77±3.42 vs. 17.47±0.78; $p<0.05$), which confirms the results shown in previous study that suggested that functional deficit, and reinforcing the executive dysfunction is a characteristic neuropsychological symptom of schizophrenia.[16] There was statistically significant positive correlation between the FAB total score and distance between corpus callosum and frontal pole in cases ($r=0.93$, $p<0.05$) showing structure-function relationship which showed better frontal structural integrity is related to better cognition. The data collected showed positive association of structural and functional deficits in the cases, coinciding with the present-day hypothesis, i.e., frontal lobe hypothesis of schizophrenia.[17] The study findings provided good support for the hypothesis that patients would exhibit a decreased distance between the frontal pole and the anterior corpus callosum and a poorer overall cognitive performance.[18]

These finding supports the neurobiological theory that says that a greater overall burden of disease is seen by increased structural abnormalities in the frontal system. Previous study has found a weak correlation of the Total PANSS Scores to general structural measures in contrast to our study which has shown a strong positive correlation with distance between corpus callosum and frontal pole in cases which suggest a strong association of disease with the changes in the PANSS.[15] The positive correlation of the total score in this study suggests that the symptomatic severity measured by the PANSS is suggests as found in earlier studies on the distance between corpus callosum and frontal pole in cases. This further aligns with the hypothesis that frontal pathology has association with clinical picture of patients of schizophrenia and its severity as detected on the CT scan. The positive correlation between the CT scan finding and lower functional assessment score in patients suffering aligns itself as proven earlier on the neurobiological mechanism.[13,14]

There are certain limitations to our study. Firstly, a longitudinal study would have helped us with better understanding of the duration related changes in the CT Scan findings in cases but that would have required a longer duration of study which was not possible as the study had to be completed in two months after approval. Secondly, the sample size could have been larger but that again required extended periods of more than two months, and a small sample size limits the generalizability of positive correlation. Thirdly, changes in the grey matter volume and white matter integrity could be better done on functional anisotropy or DTI as compared to CT scan, which gives the gross morphology of the brain, but using these parameters would have significantly affected the feasibility of the study and time duration of the study would have to be extended. Fourthly use of more diagnostic tools for the morphological imaging of brain including MRI, DTI and anisotropy could have given better correlation, but too many tools could have affected feasibility of the study and would have prolonged the study duration for the study.

Future long-term studies can be conducted using the longitudinal approach, with long follow-up of patients with involvement of more elaborative diagnostic modalities to further strengthen the correlation of functional brain damage with the symptoms of schizophrenia.

CONCLUSION

To conclude, a statistically significant anatomical-functional deficit was seen in the patient suffering from schizophrenia suggesting a positive association of short distance between corpus callosum and frontal pole as compared to healthy controls. Patients also showed significantly lower scores in the frontal assessment tests as compared to controls with a positive correlation with short distance between corpus callosum and frontal pole. The PANSS total score was positively correlated with the short distance between corpus callosum and frontal pole, signifying higher abnormality and a greater total symptom burden. This research provides locally validated, quantifiable neurobiological data from the Indian subcontinent, supporting the critical shift in psychiatry toward using objective markers for patient stratification, prognosis, and precision therapeutic planning.

Conflict of interest: None declared by the authors.

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Ethical approval: This study was approved by the Institutional Review Board (IRB) of Teerthanker Mahaveer Medical College and Research Centre, Teerthanker Mahaveer University (TMU), UP, India.

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