Turkish Journal of Medical Sciences

Volume 31 | Number 6 Article 12

1-1-2001

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Turk J Med Sci
31 (2001) 533-537

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Relationship Between Psychopathology and Regional Cerebral Blood Flow Detected by Tc-99m HMPAO SPECT in Patients with Predominantly Positive or Negative Schizophrenic Symptoms

Received: December 11, 2000

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Abstract: We investigated whether rCBF values obtained with the SPECT technique are different in schizophrenics with predominantly positive or negative symptoms and assessed the biological underpinnings of psychotic phenomena, which has been done repeatedly in the past, with somewhat varied results.

Twenty-nine schizophrenic patients were examined to investigate the relationship between regional cerebral blood flow (rCBF) and psychopathology according to SANS, SAPS and BPRS scores. Using the Tc-99m HMPAO SPECT method at rest, rCBF was assessed in 15 patients with predominantly positive (group I) and 14 with predominantly negative (group II) symptoms. Ten age-matched normal healthy volunteers comprised the control group.

We found that the rCBF of group II was prominently decreased in the temporal region compared to that of group I. Basal ganglia rCBF demonstrated a hyperperfusion pattern in medicated vs non-medicated patients ($p<0.05$). Negative symptom scores showed a positive correlation, particularly with left parietal blood flows, and a negative correlation with temporal region blood flows; positive symptom scores showed correlations positively with temporal region blood flow and negatively with left parieto-temporal blood flows.

It is suggested that positive/negative symptoms might reflect a dysfunction of fronto-parieto-temporal heteromodal association cortices.

Key Words: schizophrenia, negative/positive symptoms, SPECT.

Introduction

Recent studies of the etiology and pathogenesis of schizophrenia are characterized by an emphasis on the distinction between positive and negative symptomatology. Some SPECT/PET studies have reported diffuse hyperactivation (1), normal cerebral tracer uptake (2) in patients with predominantly positive symptoms, and prefrontal hypometabolism (3-5) and increased rCBF in the left thalamus and right basal ganglia (5) in schizophrenia with predominantly negative symptoms.

Studies related to measurement of rCBF in schizophrenic patients might reveal important data enlightening the etiology of this disease. To date, although a large amount of work has been done on symptoms generally, limited studies have been done on the measurement of rCBF, which may be helpful for etiologic subclassification of schizophrenia.

We investigated whether rCBF values are different in schizophrenics with predominantly positive or negative symptoms who had been shown to have differences in terms of clinical, biochemical and structural views in previous studies.

Materials and Methods

Subjects

Twenty-nine schizophrenic patients (21 male and 8 female) were included in the study. The diagnosis of schizophrenia was made according to DSM-IV (6) Ten aged-matched healthy volunteers (7 male, 3 female) comprised the control group. Mean ages of female and male patients were 32.8 (16-59) and 33.7 (16-52) years, respectively. Mean period of disease was 6.5 in female and 10.8 years in male patients. Seventeen patients were not taking any neuroleptic drug at least 6 weeks before the assessment time. All the subjects were

right-handed and gave their informed consent to participate in the study.

Psychopathology

For the evaluation of symptoms of patients, the Scale for the Assessment of Negative Symptoms (SANS) (7), the Scale for the Assessment of Positive Symptoms (SAPS) (8) and the Brief Psychiatric Rating Scale (BPRS) (9) were utilized. These scales' reliability and validity had been previously tested in Turkey (10,11). Assessment of global severity was made by the 18–item BPRS total score. Positive symptoms were assessed by the sum of the following four BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior and unusual thought content. In this scale "diminished emotional range", "motor retardation" and "blunted affect" sub-items were assessed as negative symptoms (12).

Imaging Protocol

Regional cerebral blood flow at rest was evaluated with the SPECT technique. 740 MBq Tc-99m-HMPAO was injected intravenously to the patients and controls. Acquisition started 15-20 min after injection. The SPECT study was performed under less lighted and quiet conditions when patients were in a resting position and their eyes were closed. The SPECT studies were performed using a gamma camera equipped with a low energy, general-purpose parallel-hole collimator, and interfaced with a computer. (General Electric-Starcam 4000-X C/T). SPECT data were collected from 64 projections with a 64x64 matrix and 1.33 zoom in circular orbit, and an energy window of 20% was selected. Projections were pre-processed using a Hamming Filter from available software, and transversal, frontal, saggital and oblique sections parallel to the orbitomeatal plane were reconstructed by filtered backprojection algorithms. Slice thickness was 1 pixel width. For quantitative evaluation, 16 regions of interest (ROI) on the 3 consecutive orbito meatal line slices (OML) were drawn. The ROIs drawn on the first OML slice were compatible with prefrontal, parietal and parieto-occipital regions. The second OML slice included the ROIs of the frontal, parieto-temporal and occipital lobes and basal ganglia. There were only 2 ROIs on the third OML slices representative of bilateral temporal lobes.

The ratios of the mean counts of these 16 ROIs to the mean counts of the whole brain were obtained. These ratios were expressed as ROI/total brain indices. The quantitative indices of the patients with negative and positive symptoms, medicated patients, drug-naive patients and controls were compared. The assessment of SPECT images was performed by two nuclear medicine physicians who were blind to the subjects' clinical status.

Statistical Analysis

The Mann-Whitney U test was used to evaluate differences between schizophrenics with positive and negative symptoms and controls in terms of mean rCBF values. We used Spearman's Rank test for correlation analysis. A stepwise multiple regression analysis was performed to control for the possible confounding influence of gender, age, and treatment of each of the patients. Statistical analyses were performed using the SPSS (13).

Results

There were 15 patients whose positive symptoms were dominant (group I: 10 males and 5 females) and 14 whose negative symptoms were dominant (group II: 11 males and 3 females). The right temporal ($p<0.01$) and left temporal rCBF ($p<0.05$) results of group I were significantly higher than those of group II. Mean rCBF values of various regions of the brain are shown in the Figure.

By stepwise regression analysis, for each patient the partial correlation factor for treatment, age, gender was very low (<0.001 to 0.1) and was not significant.

Significant correlations between SANS, SAPS and BPRS scores and rCBF measurements are given in Table. While group I had decreased values compared to both group II and the controls, decreases in the right temporal and left temporal blood flow rates were at a statistically significant level ($p>0.05$). A comparison between the rCBF values of the patient and control groups indicated that the two groups differed significantly from each other, with the patients having higher basal ganglia rCBF levels. Comparing the ROI values of all neuroleptic–naive schizophrenia patients to medicated ones, a statistical difference was found in basal ganglia rCBF levels ($p<0.05$). Controls and schizophrenics showed a difference in terms of right versus left brain hemisphere rCBF values in favor of the left side ($p<0.05$).

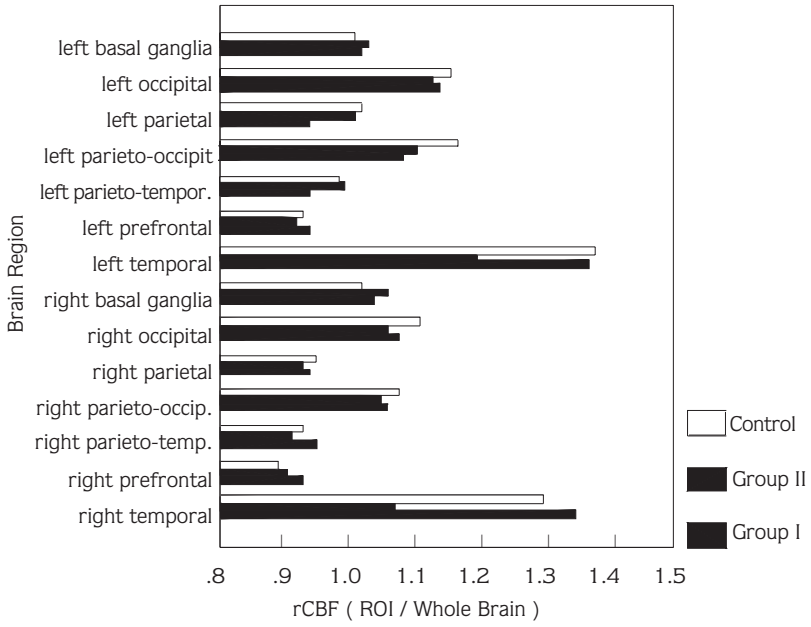

Figure. Mean rCBF values of negative and positive schizophrenic patients

Table. Correlations between psychopathological evaluation parameters and rCBF (Spearman Rank Correlation Analysis) (n=29).

	right prefrontal	right frontal	left frontal	left parietal	right parieto temp.	left parieto temp.	right temp.	left temp.	left basal ganglia
Symptoms									
Attention				.457*			-.490*		
Hallucinations							.592**		
Delusions						-.596**			
Bizarre behavior									-.478*
Total SAPS						-.595**	.593**		
Emotional withdrawal		.491*		,510*		-.500**			
Motor retardation				.514*					
Hallucinatory behavior								.613**	
Suspiciousness						-.546*			
Unusual thought content	.472*				.570*				
Excitement		.536*	.602**						

**Correlation is significant at the 0.01 level

* Correlation is significant at the 0.05 level

Discussion

We found that group II revealed bitemporal hypoperfusion, particularly in the right temporal rCBF; this finding was consistent with other studies (2, 14). Although there were studies reporting that hypofrontal rCBF in patients with negative symptoms (4,5,15), we could not detect such a finding. Guenther et al.(1986) found that schizophrenics with positive symptoms

revealed diffuse hyperactivation but we determined a local rCBF increase in the temporal region (1).

When we examined each of the psychopathology scores and rCBF correlations, negative symptoms, attention, emotional withdrawal, and motor retardation scores especially correlated positively with left parietal rCBF, and negatively with temporal rCBF. Additionally, emotional withdrawal was found to be associated with increased right prefrontal rCBF. Liddle et al.(1992) detected a relationship between psychomotor poverty and decreased left superior parietal association cortex and decreased dorsolateral prefrontal cortex rCBFs (16). Kawasaki et al.(1992) found a relationship between affective flattening severity and left middle prefrontal cortex rCBF. That patients with frontal lobe lesions show negative symptoms such as slowing of psychomotor activity, aspontaneity and lack of initiative, confirms the presence of an association between frontal rCBF and negative symptoms (17). Prefrontal and temporoparietal association cortex is a parallel network that facilitates arousal, attentional and motivation functions (18) and, in our study, that negative symptoms have an association with these three regions may indicate the possible role of these three regions on the onset of negative symptoms.

When positive symptoms were examined, we found that delusions correlated positively with right temporal rCBF and unusual thought content positively with prefrontal rCBF. Rubin et al. (14) and Sabri et al. (19) found that thought disorders were related with high rCBF in the temporal and prefrontal cortex. In our study, delusions correlated negatively with left parieto-temporal rCBF and hallucinations correlated positively with right temporal rCBF(14,19). Recently, it was reported that patients with temporal lobe lesions or dysfunctions have auditory hallucinations (20). On the other hand, some studies reported patients with a recent history of auditory hallucinations showing an atypical right temporal lobe dominance (21,22). These findings suggest that the auditory hallucinations in schizophrenia may be involved in functional hyperactivity in the temporal cortex.

Although there was a tendency for discrimination of schizophrenia as negative/positive, in our experience both symptoms usually present together in one patient. In this study, we determined that both negative and positive symptoms were related with frontal, parietal and temporal rCBF. Because different symptoms were related to different brain region rCBF levels in our study, we thought that schizophrenic symptoms might result from dysfunction of a system including frontal, temporal and parietal regions, which may be considered an heteromodal association cortex.

In conclusion, we think that schizophrenic symptoms might be related to prefrontal and temporo-parietal association cortices, particularly auditory hallucinations with temporal rCBF; but to illuminate these thoughts, more specific brain regions must be examined by using more sensitive techniques and with large patient groups.

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