18F-FDG PET/CT Evaluation of Regional Cerebral Metabolic Activities in Childhood Onset Schizophrenia

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Abstract: *Introduction:* Functional neuro-imaging with FDG PET CT in schizophrenic patients have reported certain patterns of increased or decreased metabolism in specific areas of the brain. Frontal lobe is one of the cortical areas consistently associated with schizophrenia and the activity levels have been reported to vary with the symptomatology at presentation. Predominantly positive symptoms cause and underlying hyperfrontality and negative symptoms are associated with hypofrontality. This study aims to assess the imaging patterns in unmedicated pediatric patients with a diagnosis of schizophrenia and predominantly positive symptoms.

Patients and methods: 48 pediatric patients with a diagnosis of schizophrenia (all unmedicated, 38 never medicated) and 10 healthy age-matched controls were evaluated with FDG PET CT. The patients met ICD-10 and DSM-IV criteria for schizophrenia and all reported psychotic, "positive" symptoms when tested.

Results: Children with schizophrenia and positive symptoms had a pattern of diffuse hyper-metabolism involving the bilateral frontal cortices and could be demonstrated on quantification by region to occipital ratio comparison . Associated statistically significant differences were also found when comparing ratios of occipital to thalamic, striatal and temporal cortex in these patients when compared to controls.

Conclusion: Diffuse frontal hypermetabolism or hyperfrontality is observed in children with schizophrenia when there is a predominance of positive symptoms. There could be a possible disruption of cortico-striato-thalamic feedback loops causing hyperfrontality as seen in in experimentally induced models of psychosis.

Keywords: Hyperfrontality · FDG-PET, Pediatric, Schizophrenia, Frontal lobe, Thalamus, Positive symptoms.

INTRODUCTION

Various theories to elucidate the Etio-pathological basis of Schizophrenia have been increasingly discussed in the light of neuro-developmental or neuro-degenerative pathways. Histological features correlated with clinical symptomatology points to some areas of the brain being affected more than the others. The prefrontal cortex, striatum, and thalamus form a neural circuit important in regulating sensory input, attention, and action. Deficits in these three areas in schizophrenia have been widely reported in both structural [1] and functional [2] brain imaging studies.

However, it is possible that the metabolic pattern and underlying evolutionary abnormalities could be different in pediatric schizophrenic patients and could also vary depending on their clinical presentation, symptomatology and treatment status. The symptoms of schizophrenia fall into three broad categories: positive symptoms, negative symptoms and cognitive symptoms. Positive symptoms are psychotic behavior, delusions or false beliefs ,thought disorders and movement disorders. The negative symptom constellation in schizophrenia includes psychomotor retardation, avolition, apathy, anhedonia, attentional impairment, and decreased emotional expression [3, 4]. Negative symptoms are associated with poor premorbid function, the male sex, and a low IQ [5] and are correlated with poor outcome [6]. Functional imaging with Positron emission tomography (PET) and single photon emission computed tomography (SPECT), which measure regional cerebral blood flow (rCBF) and/or metabolism, reveal a number of abnormalities and deficiencies in persons with schizophrenia, compared with healthy subjects. One of the features which have been reported in multiple studies is a lower level of prefrontal cortical metabolism in schizophrenic subjects [7] which has also been confirmed by cognitive tests indicating frontal or pre-frontal dysfunction, such as the Wisconsin Card Sorting Test [8-14] or others [15-17]. Thus hypofrontality has been related to negative symptomatology in schizophrenia [18]

In the present study in a group of drug naïve or unmedicated pediatric patients with a diagnosis of

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schizophrenia and predominantly "positive" symptomatology, we attempted to study the cerebral resting activity and metabolic pattern with FDG PET. Further attempt was made to examine other possible or consistent features such as frontal/pre-frontal dysfunction or involvement of other sub cortical structures like striatum and thalamus.

METHODS

Patient Characteristics

The study was cleared by the Institutional review board and written informed consent was obtained from the primary care givers, who were parents in majority of the subjects. In case parents were considered incompetent to give consent, the same was obtained from their grand parents or immediate relatives who were responsible for the patient's care.

Psychiatric rating evaluations were done independently by any two experienced clinicians with long experience in administering and interpreting the tests. Forty-eight patients (32 male, 16 female) who met the ICD-10 and DSM-IV criteria for schizophrenia were included in the study. Exclusion criteria included a diagnosis of mental retardation, any lifetime history of significant medical or neurological illnesses and substance use disorder. Information concerning socio-demographic variables was collected from patients or from their parents/relatives. All patients were unmedicated and thirty-eight were totally drug naïve at the time of scanning. Mean age was 15.1 years (SD 2.6), all but two were right handed. Mean duration of disorder since first onset was 18.6 (SD 11) months, age of onset 14.2 (SD 3.6) years; age at first hospitalization was 14.8 (3.8) years. Mean number of previous hospitalizations was 2.4 (SD 1.6). Mean level of education was 9.4 (SD 4.8) years.

Psychopathology

Patients with schizophrenia, were scored with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS). PANSS general score as rated by an experienced psychiatrist at baseline was 40.2 (8.1), PANSS positive score 24.6 (SD3.2), PANSS negative score 20.8 (SD 7.9). The control group consisted of 10 age- and sex-matched healthy individuals, who were relatives of oncology patients referred to our department. They were also asked to give written informed consent and had no history of psychiatric or neurological diseases and were all-free of any medication.

FDG-PET

FDG-PET scanning was performed on a Siemens Symbia 6 PET CT scanner. The scanner acquires 63 contiguous trans-axial planes, simultaneously covering 15.5 cm of the axial field of view. Data acquisition follows a standardized protocol for regional acquisition of the brain, established at the Department of Nuclear Medicine. An intra-venous injection of 120 MBq (F-18)FDG was given to each subject after over night fasting and checking of fasting blood sugar levels. This is followed by an uptake period of 30 to 45 minutes during which time the subject is placed in a dark room with no visual or auditory stimuli and encouraged to relax. The head of the subject is fixed in a head holder and adequately positioned in the gantry and then scanned with eyes closed in a moderately light environment. Acquisition starts with a diagnostic CT transmission scan used for subsequent attenuation correction. This is followed by the emission scan (3 frames, 10 minutes/ frame, 128 x 128 matrix, 3D acquisition). Images were reconstructed by iterative reconstruction using OSEM and the images were corrected for scatter and attenuation. The data obtained from the reconstructed PET images was transferred to a work station with Scenium software (Siemens) which enables one to compare the patient data after stereotactic realignment to a 3-dimensional reference template created from a normal database of 12 age matched patients. Deviations from the normal database may be assessed on the voxel-level evaluating statistical differences using the standard deviation criterion. This approach allows one to compare the baseline status in different individuals with a normal database as well as to assess the intra-subject variation in repetitive studies on the same individual. Data from the set of 63 regions of interest (ROIs) covering the whole brain were pooled and combined to separate ROIs for frontal, parietal, temporal, occipital cortex as well as striatum, thalamus, cerebellum and brainstem.

Statistics

All statistics have been calculated using the SPSS software package. Ratios between different regions and the occipital cortex have been calculated to compensate for inter-individual variation of metabolic rates. Mean and standard deviation values have been calculated for the ratios to describe the distribution of the data. Student t tests were used to compare group differences between the patient group and the control group.

RESULTS

Regional Metabolic Rates of Glucose

The schizophrenic group had higher SUV values in almost all the quantified cerebral regions. However, the standard deviation for all areas were high in both the patient as well as control group and also in all the regions of the brain. None of the differences were statistically significant, suggesting high inter-individual variation.

Thus, more attention should be paid to ratios between brain regions and the occipital cortex as reference, referred to as 'metabolic ratios'. These also play an important role in diagnosing a frontal hypo- or hyper-metabolic pattern. Table **1** gives an overview of the calculated ratios as well as their standard deviation and also illustrates differences between the patient and the control group.

The mean metabolic ratios of the patient population were higher than controls in all examined areas.

The temporal -occipital ratios differed only slightly between the patients and control groups and was (0.97 ±0.04 vs. 0.94 ±0.07). Similarly the parietal-occipital ratios for the 2 groups were not significantly different (1.08±0.06 vs. 1.06 ±0.05). However, we found a significant difference of the frontal-occipital ratio (1.11±0.07 vs.1.0 3 ±0.06, $p<0.05$), which indicates a frontal hyper-metabolic pattern. Furthermore, statistically significant differences were found for the respective ratios for striatum (1.18 ±0.05 vs. 1.09 ±0.08) and thalamus (0.99 ±0.08 vs. 0.93 ±0.04). The mean frontal-occipital ratio in patients is 11.2 % higher than that in the control group. Among all examined metabolic ratios this ratio shows the strongest difference between patients and controls.

Further attempt to look at any potential difference or asymmetrical influence between the two hemispheres revealed no significant difference in the metabolic ratios between patients and controls in the right hemisphere or left side. In addition, there were no significant difference between the metabolic ratios of any regions between the two hemispheres in each subject (Table **2**).

Table 1: Calculated Metabolic Ratios and Standard Deviations

	Patient group		Control Group	
	Mean	SD	Mean	SD
Frontal/occipital	1.11	0.07	1.03	0.06
Parietal/occipital	1.08	0.06	1.06	0.05
Temporal/occipital	0.97	0.04	0.94	0.07
Thalamus/occipital	0.99	0.05	0.94	0.05
Striatum/occipital	1.18	0.05	1.09	0.08

Table 2: Calculated Metabolic Ratios for the Two Hemispheres in the Two Groups

	Patients		Controls	
	Mean	SD	Mean	SD
r/l ratio frontal	1.2	0.04	1.1	0.03
r/l ratio parietal	1.06	0.05	1.03	0.06
r/l ratio temporal	0.87	0.06	0.97	0.03
r/l ratio occipital	1.11	0.04	1.09	0.06
r/l ratio striatum	0.9	0.07	0.9	0.05
r/l ratio thalamus	1.09	0.08	1.1	0.09

DISCUSSION

This is a novel 18 F FDG PET-CT study exploring the metabolic pattern and possible differences between a group of pediatric patients diagnosed with Schizophrenia and having predominantly “positive “ symptomatology and an age matched control population. It is important to note that the subjects were not under any drug therapy or were totally drug naïve, as drug therapy would alter the underlying metabolic pattern. The study documents widespread cortical hypermetaboilism in the patient subgroup, with the most important and consistent feature being a relative frontal hypermetabolism or “hyperfrontality”. Though a consistent or statistically significant association was not found in many of the other cortical areas like parietal or mesial temporal regions, statistically significant relative hyper-metabolic pattern was noted in various other regions like thalamus, striatum and temporal lobes. All the patients except two were right dominant, though no significant right / left asymmetries could be demonstrated. The concept of frontal dysfunction, especially decreased activation or hypofrontality has been documented in schizophrenic patients, based on numerous functional and neuro-imaging studies, especially in patients with negative symptoms [19-21).

In contrast, numerous reports also observe a relative hyperactive frontal cortex, termed hyperfrontality in animal models of ketamine or psylocybin induced psychosis [22-24]. Similarly, frontal hyperactivity has been documented in unmedicated schizophrenic patients presenting with acute episodes [25-30].

Thus, we understand that there could be increased or decreased activation in various areas of the brain depending on the symptomatology, acuteness of presentation as well as treatment history. It is possible that patients prewsenting with negative symptoms could have more suppressed brain activity, specifically decreased frontal activity levels, as shown by Andreasen *et al.* [19]. This concept was further elucidated in another study, which found consistent patterns of hypo or hyper metabolism in various cortical areas in never treated schizophrenic patients [31] using SPECT data and r CBF depending on the symptom complex of presentation. A positive correlation was found between positive symptoms and increased rCBF in various regions including the frontal cortex. It has been postulated that a frontal hypermetabolism or increased activity could be due to the disruption of the cortico-striato-thalamic feedback loops, which inturn controls the thalamic filter function leading to high levels of sensory input [32] leading to a sensory overload of the frontal cortex and its limbic relay stations.

It could be hypothesised that a pattern of reduced frontal and thalamic activation could be more associated with negative symptomatology in unmedicated schizophrenia patients while hyperactivity of these regions be observed more often in patients with more positive symptoms. However it is important to note that a similar pattern of frontal and thalamic dysfunction have also been described in acute psychosis of Bipolar etiology and alcohol hallucinosis, which closely resembles paranoid schizophrenia [33]. Thus this finding might not be specific for schizophrenia. It is illustrative to note that the observations and patterns in schizophrenic patients based on functional and neuro-imaging studies in schizophrenia have to be viewed and evaluated with caution as there a number of confounding variables which can affect findings, such as chronicity of symptoms, acuteness of the episode, drug history, patients’ psychopathology, imaging techniques, scanners and ambient status and stimulation of the patients at the time of scanning [34]. Multiple reports have demonstrated metabolic shift and realignment of imaging patterns in schizophrenic patients treated with typical or atypical neuroleptics, which demonstrate the importance of medication effects in neuro-imaging studies in schizophrenia. Reduction in frontal metabolism with attendant decrease in the metabolism of thalamus and striatum even with as single dose of the atypical neuroleptic risperidone has been documented [35-38].

In the present study, we have tried to eliminate few of the confounding factors, by including mostly drug naïve subjects, with a short duration of onset of symptoms and predominantly positive symptoms alone. In addition, the study group is a fairly uniform pediatric population from a similar socio-economic, educational and geographical background. Thus, this study could serve as an indicator for the prognostication as well as to assess the progress in children with a diagnosis of schizophrenia. Consistent finding of hyperfrontality, in the absence of long duration of illness or drug therapy or prior history of neuro-psychiatric issues, underscores the potential role of the frontal lobe in patients with positive symptomatology.

This study has to be viewed in the light of numerous limitations, few of which are the limited sample size and

lack of interventions with the addition of cognitive tasks which usually lead to an activation of the frontal lobe like the Wisconsin Card Sorting Test or others may have led to more significant results. It would be more meaningful to follow up these patients over time and medication or psychotherapy as the course and chronicity of the illnesses are typically varied. Younger patients with a small duration of illness should be further sub-classified on the basis of therapy response and functional improvement, which would be useful in studying the course of disease progression and control in different groups.

To conclude, this study indicates a metabolic pattern of underlying cortical hypermetabolism in unmedicated pediatric schizophrenia with positive symptomatology, with significant activation of the frontal, striatal and thalamic areas.

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