

Original Research Article**Functional Imaging in Depression Population - Exploring the Unexplored**

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Background: Depression is a common psychiatric illness affecting all age groups with high life time prevalence. Recurrent depressive disorder is diagnosed from second episode of depression. Psychiatry has started searching for a biological basis with recent advances in functional imaging techniques, like Single Photon Emission Computed Tomography to identify changes in cerebral perfusion associated with psychiatric illness Aim and objectives: To study cerebral perfusion changes in Recurrent Depressive Disorder subjects in different locations of brain using SPECT scan during depressive phase and in clinical remission

Material and Methods: Prospective, observational study at a tertiary care center with institutional ethics committee approval

Results: 11 subjects participated in the study with increased perfusion in Right Frontal, Temporal and Caudate nucleus and decreased perfusion in Left Parietal region following successful treatment was observed. Though regional perfusion pattern changed with treatment in different brain regions, no significant difference in regional blood flow has been noticed between pre and post treatment groups (p value > 0.05) in all regions measured.

Conclusion: There are regional variations in perfusion pattern in different brain regions, but there does not exist significant differences in cerebral perfusion before and after successful treatment with antidepressant medications.

Keywords: Recurrent Depressive Disorder, Single Photon Emission Computed Tomography, regional Cerebral Blood Flow, Ethyl Cysteine Dimer.

Introduction

Depression is a common psychiatric illness affecting both genders and all age groups with a life time prevalence of 5-17 %^[1].

Neuropsychiatric conditions are the most important causes of disability, accounting for around one third of Years Lost due to Disability among adults aged 15 years and over. Depression is the leading cause for disability both in males and females, the burden of depression is 50% higher for females than males.^[2]

Brain imaging has become an important area of psychiatric research and is beginning to influence how we understand psychiatric illness and how it should be treated. Imaging techniques such as SPECT have this potential – the challenge is to identify the clinically relevant variables significantly associated with SPECT pattern. Brain SPECT is a well-established and reliable method for evaluating brain function through measurement of regional cerebral blood flow (rCBF).^[3]

Recurrent depressive disorder is a common clinical condition where still diagnosis and management are dependent solely on clinical history. After a single episode of major depression, around 85% experience recurrent episodes. While the first episode of major depression is often provoked by a negative life event, subsequent episodes are often not precipitated by a stressor. Depressive episodes typically increase in frequency and duration as they return.

Early functional neuroimaging studies comparing healthy and depressed subjects reported decrease in regional cerebral blood flow (rCBF) and metabolism typically in the frontal and prefrontal regions, but also in temporal, parietal and limbic-subcortical structures. The role of functional imaging like SPECT has been instrumental in current research on biological basis of depression. rCBF alterations in depression generally normalize after a response to treatment with medication.

Materials and Methods

Study subjects

The study population consisted of 11 subjects suffering from Recurrent Depressive Disorder current episode Mild or Moderate Depressive episode recruited from the outpatient/inpatient population who fulfilled the DSM IV TR criteria.

Ethics and Bio safety

The study protocol was approved by the Institutional Ethics Committee of Sri Venkateswara Medical College. Informed written consent was obtained from the patient and Legally Associated Relative before enrolling into the study and confidentiality of individuals and results were maintained.

Selection of Cases

Individuals suffering from Recurrent Depressive Disorder currently Mild or Moderate depression were identified and diagnosis confirmed by DSM-IV TR. Severity of depressive episode is evaluated by administering Hamilton Rating Scale of Depression (HAM-D). All the subjects who underwent SPECT acquisition during depressive phase were followed up on monthly basis. A repeat SPECT was performed after the patient attained clinical remission.

Inclusion Criteria

1. Subjects may be male or female, between the ages of 18 to 45 years.
2. Subjects who have signed a valid written consent
3. Subjects having a diagnosis of Major Depressive Disorder, Recurrent as defined by DSM IV TR.
4. Subjects currently experiencing a depressive episode, HAM-D score >7 and <19 during acute phase and for remission must have HAM-D < 8.

Exclusion Criteria:

1. Meeting DSM IV TR criteria for any co morbid or other Axis I disorder
2. Associated abuse or dependence of drugs in the last 3 years.

3. Female subjects who are pregnant or breast feeding.

Procedure

The SPECT study was performed in the above subjects with 740 MBq (20 mCi) of Tc99m Ethyl Cysteinate Dimer (ECD) injected intravenously into the antecubital vein that was cannulated 10 min before. The metabolic process of de-esterification accounts for hydrophilic conversion of ^{99m}Tc-ECD, a perfusion-metabolic (de-esterification) coupling is needed in case of ^{99m}Tc-ECD to be trapped within Nerve cell. Thus, ^{99m}Tc-ECD would have a predominant cellular-metabolic uptake.^[4] The patient lied in the dorsal decubitus position in a room with ambient noise and light under control and patient is instructed not to sleep. No environmental stimuli were allowed to distract the patient. Thirty minutes after the injection, brain SPECT images were gathered. Radioactive urine excreted by the subject following acquisition of SPECT was disposed as any radioactive hazardous waste for the next 24 hours.

Preparation of the patient

Before arrival, patients were instructed to avoid, caffeine, alcohol, or any other drugs known to affect cerebral blood flow (CBF). Brain perfusion is sensitive to neuronal activities, hence, tracer injection is administered in a quiet room and no interaction with patients at this time is desirable, to avoid any sensorial and cognitive stimuli.

Image Processing

The Acquisition is tri dimensionally reconstructed with iterative reconstruction using Ordered Subset Expectation Maximum 2-D technique applying Gaussian filter with an intrinsic resolution of camera of 4.2 mm Full Width Half Maximum and with attenuation correction factors were applied using Chang's attenuation correction having 0.15 attenuation coefficient.

Data Analysis

For interpretation of SPECT scan of subjects, a semi Quantitative analysis using Neurogam

analysis software was performed by the mean counts per pixel in each region were measured and exported into a personal computer running a statistical analysis software package (Stat View v.4.02). The mean counts per pixel in each region, including Frontal, Temporal, Parietal, Occipital, Caudate nucleus and Thalamus regions, were compared to the mean activity per pixel in the entire cortex (whole brain).

DSM IV TR (Diagnostic and Statistical Manual IV TR)

DSM IV TR is designed for use in both clinical diagnosis and research. The diagnosis of Major Depressive Disorder requires the presence of at least five of nine symptom criteria for at least 2 weeks, one of which is depressed mood or loss of interest.

Hamilton Rating Scale for Depression

The HAM-D was developed to monitor the severity of depressive episode, the version in most common use has 17 items. Items on the HAM-D are scored from 0 to 2 or from 0 to 4, with total score ranging from 0 to 50. Scores of 7 or less may be considered normal; 8 to 13, mild; 14 to 18, moderate; 19 to 22, severe; and 23 and above, very severe. The ratings can be completed in 15 to 20 minutes. Reliability is good to excellent, particularly when the structured interview version is used.

Results

Visual Inspection of the Images

A review of the images did not reveal any occult brain disease. We observed mild asymmetry with decreased radioactivity in several regions of the cortex. However, no specific, consistent abnormalities in ECD activity were observed on any of the sagittal, coronal or transaxial images.

Table 1: Depression Subjects - Clinical Profile

S.NO	Gender	Positive Family History	Age of Onset	Total Duration of Illness (years)	No. of Episodes	HAM-D(score) Pre Treatment	HAM-D(score) Post Treatment
1	Female	Present	31	4	4	18	3
2	Female	Absent	28	2	2	18	5
3	Female	Absent	25	3	2	15	2
4	Male	Present	27	8	3	16	1
5	Male	Absent	24	2	2	11	2
6	Female	Absent	33	3	2	14	4
7	Male	Present	32	8	3	11	2
8	Female	Absent	24	2	2	10	1
9	Male	Absent	35	7	4	9	3
10	Female	Absent	29	5	3	17	2
11	Female	Absent	35	8	3	17	4

Table 2: t-Test : Pre Treatment Vs Post Treatment

Brain Region	Groups	N	Mean counts per pixels	Std. Deviation	Std. Error Mean	t-value	p value
Right Frontal	Pre Treatment	11	48.855	4.186	1.262	0.620	0.543
	Post Treatment	11	47.627	5.064	1.527		
Left Frontal	Pre Treatment	11	47.336	4.581	1.381	-0.135	0.894
	Post Treatment	11	47.582	3.891	1.173		
Right Parietal	Pre Treatment	11	52.955	4.885	1.473	1.200	0.244
	Post Treatment	11	50.600	4.301	1.297		
Left Parietal	Pre Treatment	11	53.446	4.484	1.352	0.676	0.507
	Post Treatment	11	52.227	3.956	1.193		
Right Temporal	Pre Treatment	11	37.291	8.117	2.448	-0.366	0.719
	Post Treatment	11	38.382	5.664	1.708		
Left Temporal	Pre Treatment	11	31.191	10.707	3.228	-0.998	0.330
	Post Treatment	11	35.109	7.402	2.232		
Right Occipital	Pre Treatment	11	55.091	5.359	1.616	0.612	0.547
	Post Treatment	11	53.755	4.870	1.469		
Left Occipital	Pre Treatment	11	55.955	5.953	1.795	0.423	0.677
	Post Treatment	11	55.027	4.176	1.259		
Right Caudate Nucleus	Pre Treatment	11	42.346	8.005	2.414	0.016	0.987
	Post Treatment	11	42.300	4.742	1.430		
Left Caudate Nucleus	Pre Treatment	11	41.855	6.436	1.940	0.973	0.342
	Post Treatment	11	39.700	3.543	1.068		
Right Thalamus	Pre Treatment	11	44.746	15.722	4.740	-0.234	0.817
	Post Treatment	11	45.909	4.928	1.486		
Left Thalamus	Pre Treatment	11	48.627	8.166	2.462	0.989	0.335
	Post Treatment	11	45.464	6.779	2.044		

Table 2 : when perfusion changes between pre and post treatment groups were compared no significant difference in regional blood flow has been noticed between pre and post treatment

groups (p value > 0.05) in all cerebral regions measured.

Discussion

The present prospective open label study evaluated the pattern of regional cerebral blood flow in subjects with Recurrent Depressive Disorder currently Mild or Moderate depressive episode patients using SPECT. The available literature with regards to SPECT and depression consists of studies which included patients in different clinical setting with varying severity of depressive episode. There are conflicting observations across these studies with some studies reporting an increased perfusion and other studies reporting a decreased perfusion. Moreover there is paucity of literature in the Indian context. Socio demographic profile of subjects included in the study was, 63.63% subjects were female and 36.37% were male subjects, all the subjects were married and their educational status was primary education (54.54%), secondary education (18.18%), Intermediate (18.18%) and Graduate (9.09%). Socio economic status was Low in 72.73% and Middle in 27.27% study population, no subjects belonged to upper socio economic status. Locality of individuals belonging to urban was 36.36% and Rural was 63.63%.

In the present study, subjects with Major Depressive Disorder, Recurrent were examined both during depressive phase and follow up during clinical remission. This helps to observe any change in regional cerebral blood flow differences that could be attributed to present depressive state. Individuals were included in the study only after confirmation of diagnosis by clinical evaluation and presence of previous depressive episode i.e Recurrent Depressive Disorder currently Mild or Moderate Depressive Episode fulfilling diagnostic criteria according to DSM-IV TR. Severity was assessed by Hamilton Rating Scale for Depression during Depressive episode and after clinical remission. Both the genders were included in the study with seven female subjects and four male subjects. Positive family history of Depressive illness was noticed in three subjects (one female and two male). Eight individuals were not having family history of any psychiatric illness. Five

subjects were suffering from second episode of Depression, whereas four subjects were suffering from third episode and two of them were suffering from fourth depressive episode.

The salient features of our study

- 1) Mean age of the sample was 34.09 years
- 2) Mean age of onset of illness was 29.36 years
- 3) Mean number of depressive episodes were 2.7
- 4) Family history of affective disorder was found in 27.27 % of sample population
- 5) Gender differences were observed in cerebral perfusion pattern with higher perfusion values were observed in Female subjects when compared to Male subjects in right parietal, right caudate, left parietal, left occipital and left caudate nucleus regions.

However, in our study we did observe greater variability in regional ECD activity in depressed patients. No significant differences were observed in patients during depressive phase and in clinical remission.

Few studies with Brain SPECT with perfusion agents in patients free of medication has shown hypoperfusion of the following areas: The Prefrontal area and Temporal lobes, Cingulate gyrus, and Left Caudate nucleus.^{[5][6][7]} Where as in the present study, when Perfusion pattern was compared between Right and Left brain regions, higher perfusion values were observed in patients in Right Frontal, Temporal and Caudate Nucleus compared with Left Frontal, Temporal and Caudate Nucleus during pre treatment phase. With treatment, perfusion has restored significantly in Right Frontal and Caudate Nucleus regions with no much difference on both sides during post treatment phase. In Left Temporal region though perfusion has increased on post treatment significantly, there was difference in perfusion on both sides of brain regions even in post treatment phase.

In contrast higher perfusion values were observed during pre treatment phase on both sides of brain

in Parietal region, which on successful treatment has shown decreased perfusion values in post treatment phase bilaterally. In thalamic region, perfusion has increased following treatment on Right side and decreased following treatment on left side.

While some investigators have reported specific abnormalities in regional brain activity during depression^{[8][9][10][11]}. Maes et al. failed to detect any abnormalities in the distribution of HMPAO (hexamethylpropyleneamine oxime) in depressed patients compared to controls^[12]

Clinical Correlates of SPECT Findings

Several clinical and technical reasons might explain the divergent observations in various SPECT studies in depression. For example, some studies reporting discrete rCBF abnormalities with HMPAO have included older patients who normally show more frequent rCBF disturbances^[13]. Investigations with Xenon-133 SPECT suggest that there may be an interaction of age with depressive subtype for both global and rCBF^[14]. Significant effect of normal aging on the distribution of HMPAO in healthy subjects has been demonstrated^[15]. In contrast, in the present study the patients were relatively young and without any significant effects of age on ECD activity. No significant interactions were observed between the mean HMPAO activity ratios in any brain region and age or gender^[16].

Severity of depression has also been found to positively correlate with changes in rCBF^[17]. Interestingly, in a study using IMP (iofetamine) SPECT, right temporal lobe asymmetry was observed in depressed patients compared to medically ill controls.^[8]

There is evidence of prefrontal, limbic, and paralimbic hypoperfusion in both unipolar and bipolar depression^[18] and the lateral frontal area involvement in acute depression in the elderly.^[19] Hypofrontality was shown to be associated with severe negative symptoms rCBF in depressed patients before treatment was lower than in healthy controls, and a response to medication was associated with an increase in

cerebral perfusion.^[20] Though there has been perfusion change between pre-treatment and post treatment groups, but in our study we were unable to find significant difference between these two groups

ECD is a sensitive agent for detecting abnormalities characterized by neuronal necrosis, the present study suggests that it is less sensitive as a tracer for identifying the more subtle abnormalities of functional psychiatric disorders when compared with PET scan

Conclusions

Recurrent depressive disorder is a common psychiatric condition affecting all age groups where the exact etiology is still poorly understood. SPECT scan is been explored in the field of psychiatry to find association between cerebral perfusion and the depressive disorders. In our study though cerebral perfusion changed significantly between depressive episode and following treatment it was not statistically significant to define a specific association between the severity of depression and cerebral perfusion.

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