

ORIGINAL ARTICLE

Assessment of regional cerebral blood flow in major depressive illness by radionuclide brain perfusion SPECT

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Abstract

Objective To assess the regional cerebral perfusion changes in patients with major depressive illness, with or without suicidal behavior by ^{99m}Tc-HMPAO brain perfusion SPECT.

Methods ^{99m}Tc HMPAO brain SPECT was performed in 40 subjects including 10 controls in Group A. There were 30 patients with major depression meeting the DSM-IV criteria scoring >17 on the Hamilton Rating Scale. The patients were subclassified into groups B and C. Group B included 16 patients suffering from major depression. Group C included 14 patients with major depression and attempted suicide or who had moderate to severe suicidal risk as assessed by Intent Score Scale. Semiquantitative assessment of cerebral perfusion was perfromed through a brain quantification software program. The cortex-to-cerebellum ratios were calculated in 16 ROIs drawn on coronal section in all the patients.

Results The scintigraphic evaluation of the cerebral perfusion in the Group B (non-suicidal) showed significant hypoperfusion in the prefrontal (p<0.001), orbitofrontal (p<0.01), frontal motor (p<0.01) and the temporal lobes (p<0.01). In the Group C (suicidal), significant hypoperfusion was noticed in the prefrontal (p<0.001), orbitofrontal (p<0.01) and frontal motor areas (p<0.001). The temporal lobe showed hyperperfusion (p< 0.001).

Conclusion In major depressive illness, the prefrontal, the orbitofrontal and the frontal motor areas, are markedly hypoperfused. In severe depression not associated with any suicidal behavior, there is hypoperfusion in the temporal lobes, whereas the temporal lobes are hyperperfused in suicidal behavior, with the degree of hyperperfusion related to the severity of the suicidal behaviour.

***Key words**: ^{99m}Tc-HMPAO, brain perfusion SPECT, major depression, cerebral blood flow*

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Introduction

Major Depressive Disorder (MDD) or unipolar depression is defined as a state of intense sadness or despair that has advanced to the point of being disruptive to an individual's social functioning and/or daily living activities.

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An episode of MDD is characterized by disturbance in mood, psychomotor activity, cognitive and vegetative behaviour [1]. Suicide is a potential, tragic consequence of untreated depression. The term "suicidality" refers to the occurrence of suicidal thoughts (or suicidal ideation) or suicidal behaviour. Suicidal behaviour may include acts of self-harm with a fatal (suicide) or a nonfatal (attempted suicide) outcome [2].

Depressive illness is clinically diverse, overlapping symptomatically with other psychiatric syndromes. In clinical practice, the diagnosis of depressive disorders is based on the Mental Status Examination, which includes observational assessment and neuropsychiatric interview as described in the DSM-IV diagnostic criteria for major depressive disorder [1]. Neuroimaging techniques are employed for defining the neuroanatomy and the pathophysiology of the psychiatric disorders.

^{99m}Tc-HMPAO (hexamethylpropyleneamine oxime) brain perfusion SPECT is a functional neuroimaging technique that allows three-dimensional noninvasive study of physiologic and physiopathologic events in human brain. Brain perfusion SPECT contributes to the knowledge of the pathophysiologic basis of neurological and psychiatric diseases. The ability of SPECT to detect regional cerebral blood flow (rCBF) variations in different conditions have favoured the investigation of sensory, motor, and cognitive activities (neuroactivation studies) and the central effects of central nervous system (CNS) drugs through pharmacological challenge, in both the normal and the abnormal brains [3]. Functional abnormalities in depressive disorders have been assessed with single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Both physiologic modalities provide useful data on rCBF [4].

In major depression, decreased regional CBF has been reported in the left prefrontal and both temporal regions, with the severity of depression correlating with the reduction in CBF in the anterofrontal and left prefrontal cortex [5].

Cognitive disturbance with increased negative thinking and pessimism is one of the features of the depressive syndrome. There is a relationship between rCBF, depressive symptoms and negative symptoms in patients with major depressive illness, with hypofrontality, i.e. decreased perfusion in the frontal cortex, reported to be associated specifically with severity of the negative symptoms [6].

Suicidal behaviour is one of the cognitive disturbances associated with the depressive disorders [7]. Decreased prefrontal cortex activity with increased or decreased temporal lobe activity is often the most serious subtype of the depression and it is associated with sadness, irritability and suicidal behaviour [8].

This study aimed at assessing regional cerebral perfusion in patients with major depressive illness, with or without suicidal behaviour by ^{99m}Tc-HMPAO brain perfusion SPECT.

Subjects and Methods

A normal database was created from a sample of 10 normal subjects (6 males and 4 females; mean age 27.6 ± 4.3 years). The normal controls included subjects without a neurological or psychological disorder or any psychiatric manifestations. The disease sample comprised of 30 patients (mean age 36.5 ± 9.47 years) with MDD, who fulfilled the DSM-IV criteria with a Hamilton Depression Rating Scale (HAM-D) score above 17. It was a hospital-based sample, including outdoor and indoor patients from the psychiatry department.

The patients' diagnosis was established through detailed psychiatric, neurological and psychomotor evaluation by a consultant psychiatrist. The disease sample was further categorized into groups B & C. Group B included 16 patients (38% male, 62% female; mean age 40.2 ± 8.92 years) with MDD but

without a history of suicidal behaviour, as assessed on the Intent Score Scale and the Risk of Repetition Scale. Group C included 14 patients (all males; mean age 32 ± 8.6 years) with MDD associated with suicidal behaviour. Suicidal behaviour was rated as low, moderate or high suicidal risk as assessed by the Intent Score Scale and Risk of Repetition Scale (ISS). The study was approved by the hospital ethics committee.

All subjects were instructed to avoid caffeine and tobacco 12 hours prior to the scan but the patients were not told to stop antidepressant medications. Prior to the examination, informed consent was taken from all the patients and the procedure was briefed to relieve their anxiety. Intravenous access was secured at least 10 min prior to injection with the patients lying in a quiet, dimly lit room. Ceretec™ kit (HMPAO) by GE Healthcare Ltd. UK, was used for the brain perfusion imaging. The kit was labelled with 99mTc according to the manufacturer's protocol [10]. A dose of 555 MBq (15 mCi) was injected into each subject within 30 minutes from kit reconstitution. The subject was positioned supine with the canthomeatal line perpendicular to the face of the detector and the head held straight [11]. A single-headed ECAM gamma camera system (Orbiter, Siemens) fitted with a low-energy high-resolution collimator interfaced with ICON software (version 6.0.3) was employed. The data set comprised of 64-projection acquisition (30-sec/view). For reconstruction of the raw images, 1-pixel-thick slices were obtained and processed (Butterworth filter, cutoff 0.3 cycles/cm). Brain quantification program in the ICON software was employed for semiquantitative analysis. 3-pixel-thick slices were selected along the occipitofrontal plane. Coronal slices were selected for processing as this approach gives the best separation of cortical regions and better visualization of regions showing abnormal cerebral blood perfusion [12, 13]. The fifth (parietal and cerebellar regions), ninth (frontal and temporal regions) and twelfth (prefrontal and orbitofrontal regions) coronal slices were selected. A total of 16 regions-of-interest (ROIs) were generated on each slice. The mean value of average counts was calculated in the ROIs representing the cerebellar region. In all the three slices, the average cortex-to-cerebellum perfusion ratios were calculated for each ROI.

The results of the patients were compared with the normal controls. Statistical certainty of 95% (± 2 SD) values in each ROI was set as criteria for categorizing the respective ROI as hypoperfused or hyperperfused in groups B and C. The significance of the results was evaluated by applying student's *t*-test [14].

Results

All of the semi-quantitative data was assessed for its distribution in the randomly selected ROIs from the control and disease groups. Figure 1 shows the brain perfusion images for the subjects in groups A, B and C. Since the sample was parametric, the data was seen to follow the normal distribution. In the control group (Group A), cortex-to-cerebellum perfusion ratios with 2 standard deviation (±2SD) values were calculated for each ROI.

In Group B (severely depressed patients without suicidal behavior), significant hypoperfusion was noticed in both the prefrontal areas ($p<0.001$ on both sides), the orbitofrontal areas ($p<0.01$ on the right, $p<0.001$ on the left), both frontal motor areas ($p<0.05$ on the right, $p<0.01$ on the left), both temporal lobes ($p<0.01$ on the right, $p<0.001$ on the left). Figure 4 gives the graphical representation of the overall hypo and hyperperfusion tendencies in the Group B in each of the cerebral regions under study.

Group C (severely depressed patients associated with the suicidal behaviour) patients showed significant hypoperfusion in the prefrontal ($p<0.001$ on both sides), the orbitofrontal ($p<0.01$ on the right, $p<0.002$ on the left) and both frontal motor areas ($p<0.001$). Significant hyperperfusion ($p<0.01$) was observed in the temporal lobes bilaterally. Figure 5 is a graphical representation of the overall hypoperfusion and hyperperfusion

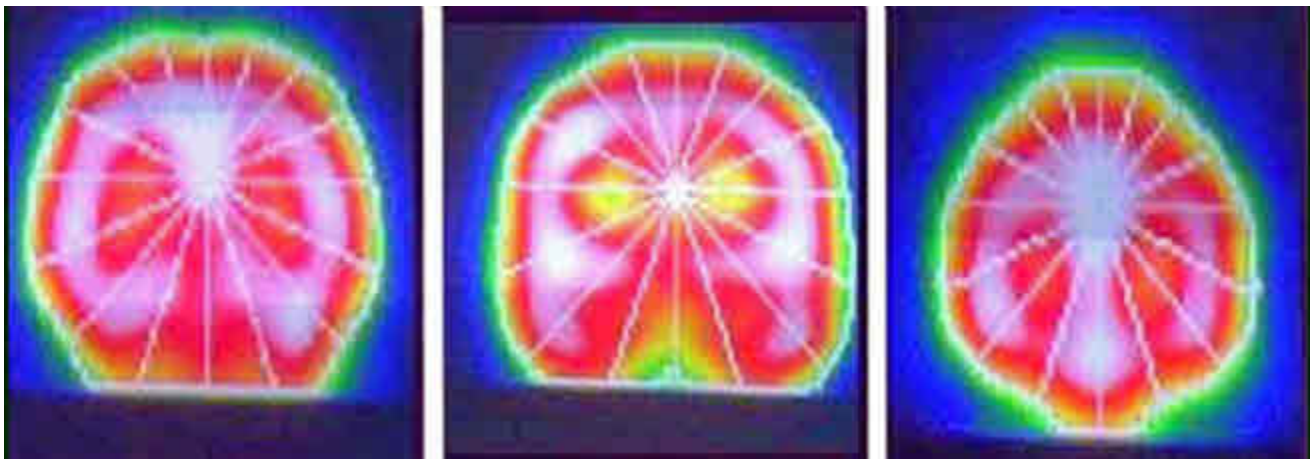

Figure 1 *Representative ^{99m}Tc-HMPAO Brain Perfusion SPECT scan of a Group-A subject (normal control)*

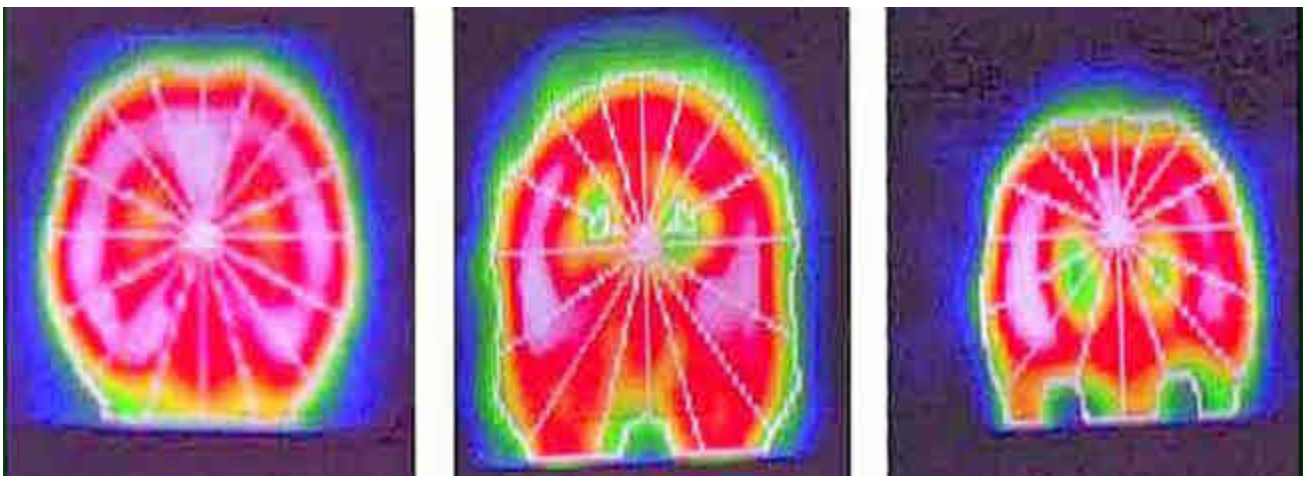

Figure 2 *Representative ^{99m}Tc-HMPAO Brain Perfusion SPECT scan of a Group-B subject (major depressive illness without suicidal behaviour)*

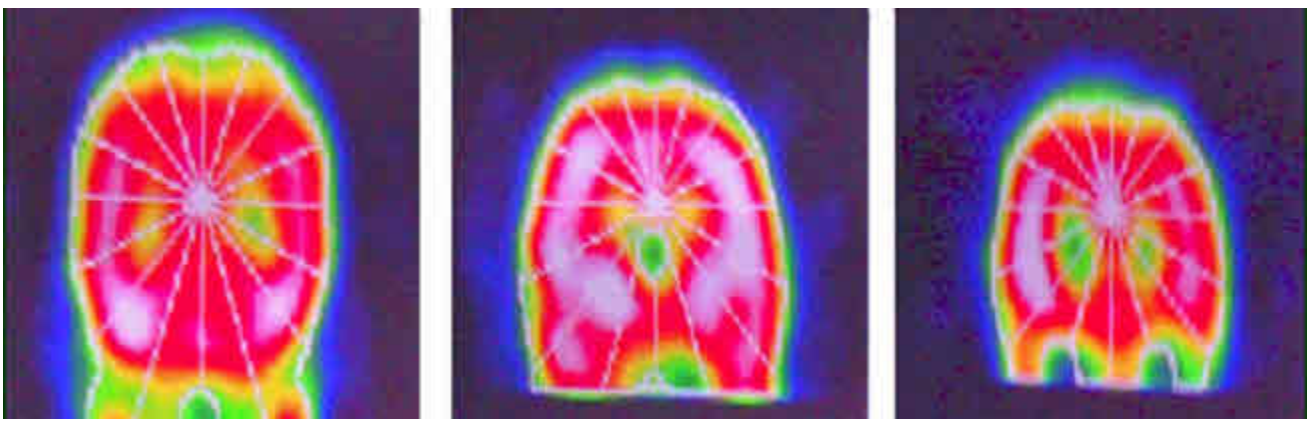

Figure 3 *Representative ^{99m}Tc-HMPAO Brain Perfusion SPECT scan of a Group-B patient (major depressive illness with suicidal behaviour)*

tendencies in the cerebral regions in Group C.

All the 30 subjects enrolled in the study were evaluated for any correlation between the scintigraphic results and the clinical evaluation on the Mental Status Examination. The comparison of the regional cerebral perfusion ratios in both the groups with the ISS score showed significantly different results in the temporal lobes. The lower score on the ISS presented with hypoperfusion in the temporal lobe, while hyperperfusion in the temporal lobe was noticed in patients scoring high on the ISS score, as presented in the Figure 6.

Discussion

The depressive disorders are one of the most prevalent psychiatric conditions in the world. A recent study by the World Health Organization found major depression to be the

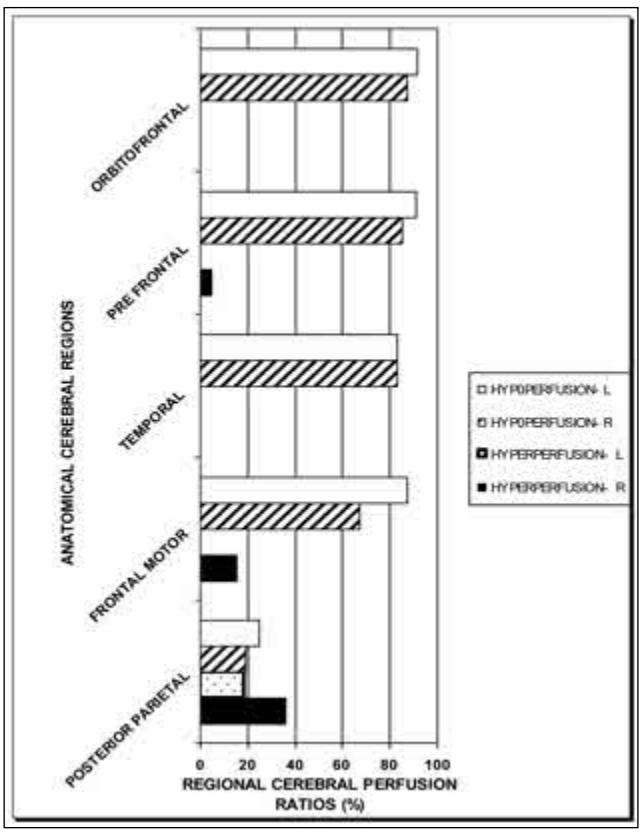

Figure 4 *Cerebral perfusion pattern in the Group B (major depressive illness) showing hypoperfusion in the prefrontal, orbito frontal, frontal motor and the temporal*

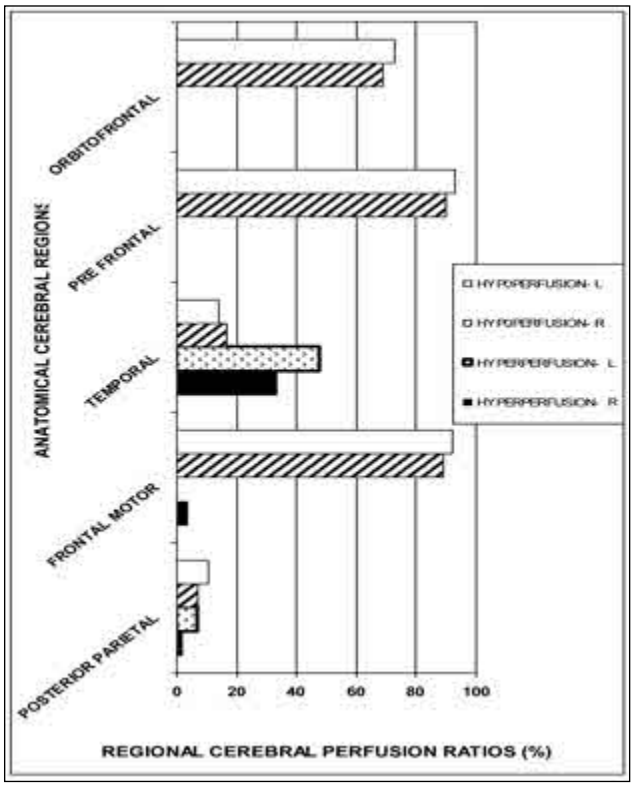

Figure 5 *Cerebral perfusion pattern in Group-C (major depressive illness with suicidal behaviour) showing hypoperfusion in the prefrontal, orbitofrontal and frontal motor areas, with the temporal lobes showing hyperperfusion*

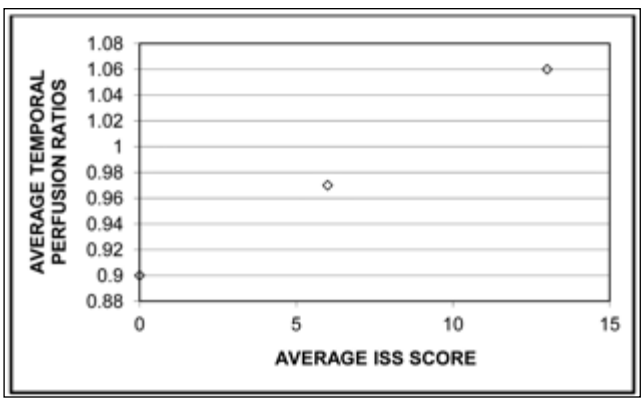

Figure 6 *Intent Score Scale and Risk of Repetition Scale (ISS score) versus temporal lobe perfusion ratios. Note that the hypoperfusion in the temporal lobe corresponds to the lower score on the ISS, whereas hyperperfusion in the temporal lobe is noticed in patients scoring high on the ISS score*

leading cause of disability worldwide. Suicide is the most dreadful complication of the major depressive disorders with 80% of suicides carried out by persons with depressive illnesses. Although there is ongoing research on mood disorders, there is however a paucity of data available on the suicidal behaviour especially in this part of the developing world.

Biochemical, pharmacologic and brain imaging techniques have all been used to study the neurobiology of mood disorders. However, because of the diverse clinical nature and overlap of symptoms with other psychiatric syndromes, the knowledge of the underlying pathology in in mood disorders remains sketchy [15].

The aim of this study was to document the cerebral perfusion changes in major depressive illness in order to determine the role of brain perfusion SPECT imaging for evaluating the underlying pathophysiology in the major depressive illness.

Although a discontinuation of antidepressants is desirable to rule out any drug effects on the cerebral blood flow. However, it wasn't ethically feasible to withdraw medications in our study population, given the risk of deterioration in symptoms in the severely depressed patients, particularly in the those associated with suicidal behaviour. A careful record of the type, dosage and duration of medications being taken by the patients was made and the patient preparation instructions ensured that there was no intake of tea or coffee and that the patient refrained from smoking 12 hours prior to the scan in compliance with the guideline procedure [16].

The gender distribution in Group B (non-suicidal) was 37% males and 63% females (ratio 1:1.7). The almost double the number of females is supported the high incidence of depression in the female gender [20]. However, Group C (suicidal) showed predominance of the male subjects (100%). This could be a biased sampling but also consistent with the statistical gender distribution in the violent behaviour. Gender is a very strong predictor of violent behaviour and of suicide. Victimization surveys have generally supported the predominance of males committing suicide [18]. The average age in the Group B was 40.2±8.92 SD with a younger average age of 32±8.6 SD in Group C.

In our study population, hypoperfusion in the frontal cortex was seen in both groups with severe depression, i.e. both without and with suicidal behaviour. Likewise, temporal lobe hypoperfusion was also seen in both the groups. However, the the Group C patients with associated suicidal behaviour showed temporal lobe hyperperfusion in contrast. The hypoperfusion in the prefrontal, the orbito frontal cortex and the frontal motor cortex, is consistent with the findings of previous studies. Drevets [4] identified neurophysio logical abnormalities in multiple areas of the orbital and medial prefrontal cortex, the amygdala and related parts of the striatum and thalamus in patients with mood disorders.

Yazici *et al.* also found decreased rCBF in the left prefrontal and in both temporal regions in major depression, with the severity of depression correlating with the reduction in rCBF in the regions of the anterofrontal and left prefrontal cortex [5]. Mozley *et al.* opined that the regional cerebral distribution of ^{99m}Tc-HMPAO demonstrates heightened variability in depressives. Asymmetries are more pronounced in the regions of the limbic system [19].

The hypoperfusion in the frontal lobe can be explained on the basis of the neurocircuitry involved in the depressive disorders. Review of the diagnostic criteria of DSM-IV for major depression shows that a large number of symptomatologic presentations are associated with brain areas involved with human behaviour, corresponding to circuits that begin in the prefrontal dorsolateral cortex, orbito-frontal cortex and anterior cingulate gyrus [14]. The dorsolateral prefrontal cortex along with its subcortical connections is defined as the superior intelligence area. The prefrontal cortex is related to the control of pleasure, pain, anger, rage, panic, aggression (fight-

flight-freeze responses) and basic sexual responses [20]. Dysfunction of the subcortical frontal circuit is related with the appearance of poor organizational strategies, inability to feel and express emotions and difficulty for keeping or changing behaviours [14]. The orbitofrontal subcortical circuit relates with characteristics of personality. Because of its functions in emotion and reward, the orbito-frontal subcortex is considered to be a part of the limbic system and has got afferences from the temporal lobe, thalamus, amygdala, and substancia nigra [14]. The orbitofrontal cortex is involved in controlling and inhibiting impulsive actions, and lesions to this area may result in disinhibited aggressive or suicidal behaviour [18] as seen in the suicidal behaviour group in our study.

Cognitive disturbances with increased negative thinking and pessimism are one of the features of the depressive syndrome. A study of the relationship between rCBF, depressive symptoms and negative symptoms in the patients with major depressive illness showed that hypofrontality, i.e. decreased perfusion in the frontal cortex, is associated specifically with negative symptom severity [6].

The limbic system is called as the "emotional brain". It influences many aspects of emotional behaviour via its connections with the hypothalamus and with the autonomic system. It is known to be involved in the depressive disorders along with a decrease in the rCBF in the prefrontal cortex as well as para limbic areas [21]. The only explanation to the hypoperfusion in the frontal motor areas is on the basis of the recent anatomic and functional data. It has been shown that each frontal motor area has a specific pattern of anatomic connections with the prefrontal lobe, and the cingulate cortex (limbic system). By virtue of its specific connections with the prefrontal and the cingulate areas, it is involved in higher-order aspects of motor control related to motivation, memory and cognitive functions that are disturbed in the depressive disorders [22]. The temporal lobes harbour the two limbic structures within its medial part: the amygdala and the hippocampus and control the emotional stability [23]. This forms the basis of hypoperfusion in the temporal lobe in the depressive disorder.

Group C patients (depressed patients with associated suicidal behaviour interestingly showed varying results in the temporal lobes. A few patients had marked hyperperfusion, while others had moderate hyperperfusion in the temporal lobes. Out of 14 patients, only 5 fulfilled the criteria of the high suicidal risk scoring >11 on ISS. On the scintigraphic perfusion assessment, significant hyper perfusion ($p<0.01$) was observed in the temporal lobes bilaterally. The rest of 9 patients with moderate suicidal risk (scoring 4-10 on the ISS), showed moderate hyper perfusion ($p<0.05$) in the temporal lobes. These two categories were restricted to the same group because of the limited number of patients in both the categories.

Decreased prefrontal cortex activity with increased or decreased temporal lobe activity is often the most serious subtype of depression and is associated with sadness, irritability and suicidal behaviour [8]. In a PubMed database search (1992-2002), an incidental finding of increased perfusion in bilateral temporal lobes was reported in depressed patients with suicidal behaviour on the resting state ^{99m}Tc-HMPAO SPECT [9]. No other specific data is available in this context. Furthermore, literature on aggression points to a dysfunction of parts of the limbic system, particularly the amygdala and the hippocampus. These two limbic structures within the temporal lobe modulate behaviour, and dysfuntioning of the limbic system results in moodiness, irritability, clinical depression, increased negative thinking, decreased motivation, flood of negative emotions and social isolation [18].

The presence of relatively greater hypoperfusion in the left cerebral cortex can be related to the dominant hemisphere phenomenon, which controls handedness, language perception, speech and the behaviour. As more than 90% of the population is right handed, the left hemisphere

is dominant [24]. There is also evidence that the frontal and temporal abnormalities associated with the violence may be expressed more in the dominant hemisphere [18].

The perfusion differences in the cerebral regions between the severely depressed patients and those with the associated suicidal behaviour were compared. Both the group showed marked hypoperfusion in the pre frontal, the orbitofrontal and the frontal motor cortex. No significant difference was found in these areas on the intergroup comparison. The comparison of temporal lobes exhibited significant results ($p<0.0001$ on both sides). The result can be attributed to the behaviour of the limbic system harbouring the temporal lobes as explained earlier. Hyperactivity was observed in the temporal lobes in suicidal behaviour depending on the severity of the suicidal risk. Whereas the severe depression not associated with any suicidal behaviour demonstrated the hypoactivity in the temporal lobes.

All the 30 subjects enrolled in the study were evaluated for any correlation between the scintigraphic results and the clinical evaluation on the Mental Status Examination, i.e. Intent Score Scale and Risk of Repetition Scale (ISS scrore). Comparison of the regional cerebral perfusion ratios with the ISS score showed significantly different results in the temporal lobes in the two groups. The lower score on the ISS, presented with hypoperfusion in the temporal lobe: the average ISS score in Group B was 0. In contrtast, hyperperfusion in the temporal lobe was noticed in patients scoring high on the ISS score (average score 8.71 ±4.04 SD), thus showing that the hyperactivity in the temporal lobe increases with the severity of the negative symptoms.

Conclusion

The results of our study show that in major depressive illness (both with or without associated suicidal behaviour), the prefrontal, the orbitofrontal and the frontal motor areas are markedly hypoperfused. In severe depression without associated suicidal behaviour, there is hypoperfusion in the temporal lobes whereas temporal lobe hyperperfusion is observed in severely depressed patients with associate suicidal behaviour, with the degree of hyperperfusion depending on the severity of the suicidal risk.

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