行政院國家科學委員會補助專題研究計畫期中報告

停經憂鬱症婦女之腦血流及多巴胺受體功能檢查(2/3)

Functional brain evaluation with Tc-99m HMPAO SPECT

and I-123 IBZM SPECT in postmenopausal depression

計畫類別：個別型計畫

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☐國際合作研究計畫國外研究報告書一份

執行單位：國立成功大學醫學系核子醫學科

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Abstract

Objectives: The brain dopaminergic change in post-menopausal women with depression is an issue still not fully explored. The purpose of this study was to evaluate the basal ganglion D2 receptor density in post-menopausal women with depression using single photon emission computed tomography (SPECT). Methods: 17 post-menopausal women, aged 42-65 years (mean 53 years), with depressive symptoms were included in this study. Four were determined to have major depression. 13 patients without depression were studied as controls. None of the patients were under anti-depressive medication. Each patient received Hospital Anxiety and Depression test (HAD) and Mini-Mental Status Examination (MMSE) to determine their level of anxiety and depression and to test their cognitive functions, respectively. Serum FSH and E2 levels were determined by IRMA for each patient. Brain MRI was performed for each patient. D2 receptor density was measured by the SPECT using $^{123}$I-iodobenzamide ($^{123}$I-IBZM). Images were acquired using a triple-headed rotating gamma camera 2 hours after injection of 5 mCi of $^{123}$I-IBZM. For the semiquantitative analysis, the basal ganglion/frontal cortex (BG/FC) ratio was calculated. Results: there was no significant difference in BG/FC ratio between depressive and non-depressive women, both by psychiatric diagnosis or by symptomatic scores. Depressive scores were negatively correlated with age ($r=0.53$, p=0.029), and positively correlated
with anxiety scores ($r=0.74, p=0.001$). FSH, E2, and MMSE results were not related to depression scores. Conclusion: On the contrary to most previous studies in major depression that showed an increase of D2 receptor density in basal ganglion, the current study shows no significant difference between depression and non-depression postmenopausal women. Different mechanisms could be involved between major depression before and after menopause. However, small sample size of this study may account for this insignificance. We will continue further investigation of this topic in this year.

**Key words:** Depression, menopausal women, Dopamine D2 receptor, $^{123}$I-IBZM SPECT

**Background**

Depression is a major health concern not only because of personal distress, excess mortality, impaired interpersonal relationships, and restriction of work activities but also because of the economic burden it imposes. The relation between menopause and depression has been hypothesized to be biological, psychological or environmental. The biological hypothesis is estrogen deficiency resulting from cessation of menstruation causes increased vasomotor and somatic symptoms or changes in the elevation of neurochemicals such as plasma serotonin, tryptophan, dopamine, noradrenaline and their metabolites that could result in increased likelihood of depression. Since the mid 1960s the biological basis of depression has been dominated by the monoamine hypothesis, focusing in particular on the involvement of 5-hydroxytryptamine (5-HT) and noradrenaline. The substantial evidence implicating dopamine in the etiology of Parkinson’s disease and schizophrenia has overshadowed the possible involvement of this monoamine in depression, but several recent studies point to involvement of dopaminergic mechanism in depressives. First, a reduced turnover of dopamine, determined by the measurement of homovanillic acid (HAV) in cerebrospinal fluid, has been demonstrated in depressed patients, particularly if motor retardation is
present. HVA concentration has been demonstrated to be lower in the CSF of depressed patients compared to controls particularly in studies that have used probenecid, implying reduced central dopamine turnover. The concentration of the dopamine metabolite DOPAC (dihydroxyphenylacetic acid) has also been reported to be lower in the CSF of depressed patients. The lower concentration of dopamine metabolites is of similar magnitude to the reduction in CSF 5-hydroxyindoleacetic acid (5-HIAA) in depressed patients.

Secondly, many antidepressants, such as tricyclics, monoamine inhibitors, nomifensine, bupropion and electoro-convulsive treatment, exhibit direct or indirect dopamine enhancing effect. Moreover, some agents with mainly dopaminergic effects, amphetamine, pirebidil and bromocriptine, may have antidepressant action. Thirdly, the mesolimbic dopaminergic system with its projections to medial frontal cortex has been implicated in depressive behavior in humans and in animal models of reward-seeking behavior. In the human brain, the anterior cingulate is densely innervated by dopaminergic neurons. With the recent advance of imaging techniques, brain function can be studied non-invasively to elucidate the underlying pathophysiology of depressive disorders. Only recently, SPECT studies with I-123 IBZM, a benzamide derivative with high D2 receptor selectivity, have been applied to study the functional abnormalities for patients with primary major depression. However, they have not been used for studying depression in menopausal women.

**Purpose**

We design this study to do single photon emission tomography (SPECT) with the dopamine D2 ligand I-123 IBZM in 30 patients with menopausal depression and compare their IBZM binding in the basal ganglia with 30 matched healthy controls. We assume that (1) there will be a significant excess of binding in the basal ganglia in depressed patients. (2) This abnormal
binding will be correlated with psychomotor function and severity in depressed patients.

**Patients and methods:**

Seventeen postmenopausal women, aged 42-65 years (mean 53 years) suspected to have depression clinically were referred from Department of Obstetric and Gynecology at National Cheng-Kung University Hospital. Four were determined to have major depression. 13 patients without depression were studied as controls. None of the patients were under antidepressive medication. Patients with a history of seizure disorder, major head trauma, cerebral vascular disease, cardiovascular disease, or a neurological disorder were excluded. Patients receiving a neuroleptic, analeptic or anticonvulsant drugs were also excluded. Serum E2 and FSH levels were determined to ensure postmenopausal status. Each patient received Hospital Anxiety and Depression test (HAD) and Mini-Mental Status Examination (MMSE) to determine their level of anxiety and depression and to test their cognitive functions, respectively. Brain MRI was performed for each patient.

**123I-IBZM SPECT**

For 123I-IBZM SPECT examination, every patient was given an intravenous injection of 5 mCi 123I-IBZM (Institute of Nuclear Energy Research, Taiwan). The IBZM binding was assessed by SPECT 2 h later. The patient's head was immobilized with a comfortable molded head holder while in the scanner. Patients were aligned with the orbitomeatal lines parallel to the detector rings. A rotating three-head gamma camera with a fan-beam collimator (Multi SPECT 3, Siemens, Germany) and a commercially available computer system were used for data acquisition and processing. Data were collected for 60 projections (360° rotation) on a 128 × 128 matrix. The acquisition time was 40 sec-per projection. Attenuation correction was performed in selected transverse slices according to "Chang's method"

Every patient received a brain magnetic resonance imaging (MRI, 1.5
Tesla, Siemens, Iselin, NJ) study. The purposes of the MRI study were: (1) to exclude structure abnormalities that cause depression, such as vascular depression; (2) to serve as a template for the determination of regions of interest (ROIs) for $^{131}$I-IBZM SPECT.

**Interpretation**

A visual examination of each subject’s scans was performed by a nuclear medicine specialist who is expert in SPECT imaging and who has no prior knowledge of the diagnosis. The images of depressed patients and control subjects will be presented at random to the reader. The digital images in the transaxial, sagittal and coronal planes will be displayed on the monitor.

**Data analysis**

For semiquantitative evaluation of specific striatal binding, ROIs were drawn manually on the basal ganglia (isocontour ROIs with a threshold of 80% of the striatal maximum) and the frontal cortex. The size of all ROIs was at least twice full-width-half-maximum (FWHM = 8.5 mm). The ratio of basal ganglia to frontal cortex (BG/FC) activity was calculated. BG/FC ratios were expressed as mean ± standard deviation. The values of left and right BG/FC ratios were combined and averaged.

**Statistics**

Data were analysed with SPSS (version 8) for the PC. Comparisons for the two groups was made by independent sample T-test. Correlations between HAD scores, serum tests and striatal tracer uptake were done by Spearman's one-tailed correlation coefficients. The significance level was set at $P < 0.05$.

**Results**

The clinical characteristics and $^{131}$I-IBZM uptake ratios (BG/FC) are summarized in Table 1. There is no significant difference of BG/FC ratio between depression and non-depression postmenopausal women. When divided by depressive severity (HAD>11 and HAD < 11), the difference of BG/FC ratio between more depressive and less depression is also not significant. (Table 2) Depressive
scores were correlated with age (p=0.029; Fig 1), and anxiety scores (p=0.001; Fig 2). FSH, E2, and MMSE results were not related to depression scores.

All the $^{123}$I-IBZM SPECT examinations were performed without significant adverse events noted by patients or physicians. Only a few patients reported a painful sensation during the intravenous injection of $^{123}$I-IBZM.

Discussion

Most previous SPECT studies with I-123 IBZM have demonstrated increased striatum uptake in depression compared with controls, if not all, suggesting either a reduction in the competition from endogenous dopamine or an up-regulation or increased affinity to IBZM of D2 receptors. Another study found IBZM binding to be specifically higher in patients with clinically rated psychomotor retardation. IBZM binding was reduced after successful pharmacological treatment and a concomitant improvement in motor retardation. The same pattern of change in IBZM binding was found in depressed patients with a successful antidepressant response to total sleep deprivation. On the contrary to most previous studies in major depression that showed an increase of D2 receptor density in basal ganglion, the current study shows no significant difference between depression and non-depression postmenopausal women, both by diagnosis or by symptoms. Different mechanisms could be involved between different groups of depressive patients. This study was design specifically for postmenopausal women who developed depressive symptoms after menopause. The hypothesis is estrogen deficiency resulting from cessation of menstruation causes changes in the elevation of neurochemicals such as plasma serotonin, tryptophan, dopamine, noradrenaline and their metabolites that could result in increased likelihood of depression. The mechanism is quite different from depression occurred before menopause.

However, small sample size of this study may account for this insignificance.
We will continue further investigation of this topic in this year. Like most functional imaging studies of depression, this study involved a relatively small sample size. This design limitation coupled with the subtle magnitude for the BG/FC differences between depressives and controls relative to the variability of such measures reduces the sensitivity of studies for detecting intergroup differences and for replicating findings across studies. Consequently, subject selection criteria that reduce the variability of imaging measures are often required to improve statistical sensitivity.

Another limitation is the clinical heterogeneity inherent within the depressive syndrome, as diverse signs and symptoms may have distinct neurophysiological correlates. For example, a depressed patient exhibiting prominent anxiety, obsessive ruminations, insomnia, and psychomotor agitation may show dissimilar imaging findings from one who predominantly manifests apathy, inactivity, excessive sleep, and psychomotor slowing. However, few studies have had sufficiently large subsamples of depressives manifesting clinical factors to sort out the relative contributions of each factor to the variability of imaging measures.

Major depressive syndrome is heterogeneous with regard to etiology and pathology. Biological heterogeneity is evidenced by the variety of antecedents to depressive syndromes; the diversity of responses to somatic or psychological therapies; and the variable presence of neuroendocrine, neurochemical, and circadian rhythm disturbances in depressive samples. If depression is associated with multiple pathophysiological states, it can be presumably be characterized by an assortment of distinct functional imaging abnormalities.

Finally, the current study is not finished yet. We will collect more cases and complete this topic in this year. We hope the further investigation will be more fruitful.

References:


Table 1. Clinical characteristics and D$_2$ receptor density of basal ganglion in women with depression and nondepression

<table>
<thead>
<tr>
<th></th>
<th>Depression (n=4)</th>
<th>Nondepression (n=13)</th>
<th>P-value</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
<td>Age</td>
<td>52.00</td>
<td>2.71</td>
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<td>FSH</td>
<td>69.18</td>
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<tr>
<td>E2</td>
<td>13.25</td>
<td>12.42</td>
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<tr>
<td>Anxiety scale</td>
<td>10.50</td>
<td>4.04</td>
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<tr>
<td>MMSE scale</td>
<td>26.00</td>
<td>1.83</td>
<td>25.54</td>
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<tr>
<td>BG/FC ratio</td>
<td>1.82</td>
<td>0.21</td>
<td>1.82</td>
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</table>

BG/FC ratio : Basal ganglion / Frontal cortex ratio of $^{123}$IBZM SPECT

Table 2. Clinical characteristics and D$_2$ receptor density of basal ganglion in women with more depressive scores (HAD $\geq$ 11) and less depressive scores (HAD < 11)

<table>
<thead>
<tr>
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<th>Depression (n=3)</th>
<th>Nondepression (n=14)</th>
<th>P-value</th>
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<td>SD</td>
<td>Mean</td>
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<td>E2</td>
<td>8.10</td>
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<tr>
<td>Anxiety scale</td>
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<td>6.50</td>
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<tr>
<td>MMSE scale</td>
<td>25.67</td>
<td>2.08</td>
<td>25.64</td>
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<tr>
<td>BG/FC ratio</td>
<td>1.77</td>
<td>0.12</td>
<td>1.83</td>
</tr>
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</table>

BG/FC ratio : Basal ganglion / Frontal cortex ratio of $^{123}$IBZM SPECT
Table 3. Correlations of characteristics and BG/FC ratio

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>FSH</th>
<th>E2</th>
<th>Depression</th>
<th>Anxiety</th>
<th>MMSE</th>
<th>BG/FC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>*</td>
<td>0.850</td>
<td>0.314</td>
<td>0.029</td>
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<tr>
<td>FSH</td>
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<td>*</td>
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<td>E2</td>
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<td>*</td>
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<tr>
<td>Depression</td>
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<td>0.952</td>
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<td>0.001</td>
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<tr>
<td>Anxiety</td>
<td>0.044</td>
<td>0.038</td>
<td>0.895</td>
<td>0.001</td>
<td>*</td>
<td>0.468</td>
<td>0.709</td>
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<td>MMSE</td>
<td>0.717</td>
<td>0.451</td>
<td>0.426</td>
<td>0.694</td>
<td>0.468</td>
<td>*</td>
<td>0.410</td>
</tr>
<tr>
<td>BG/FC ratio</td>
<td>0.429</td>
<td>0.199</td>
<td>0.049</td>
<td>0.262</td>
<td>0.709</td>
<td>0.410</td>
<td>*</td>
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</tbody>
</table>

BG/FC ratio: Basal ganglion / Frontal cortex ratio of $^{123}$IBZM SPECT
Fig 1. Correlation of age with depressive scores from HAD

![Graph showing correlation between age and depressive scores.](image)

- $R^2 = 0.2807$
- $P = 0.029$

Fig 2. Correlation of anxiety scale with depressive scores from HAD

![Graph showing correlation between anxiety scale and depressive scale.](image)

- $R^2 = 0.5535$
- $P = 0.001$