一、計畫緣起與目的

Among the neurodegenerative disorders, idiopathic Parkinson’s disease (PD) is an important one because it is a common and treatable disorder. The prevalence rate of PD at Kinmen (金門) is reported to be 587.5/100,000 for persons over 50 years old and that at Ilan (宜蘭) is 463/100,000 for persons over 40 years old [1,2]. The primary deficit of PD lies in the presynaptic dopaminergic neuron in the substantia nigra. The cardinal symptoms and signs of PD include rest tremor, bradykinesia, rigidity, and postural instability.

Discrimination between PD and “Parkinsonism-plus” syndromes is important because of differences in response to treatment and prognosis. An important point for differentiating PD from “Parkinsonism-plus” syndromes is response to levodopa. Striatal dopamine D2 receptors play a crucial role in the response to levodopa or dopamine agonist. Traditionally apomorphine test is used to predict dopaminergic responsiveness and is reported to have a sensitivity in the order of 90% [3]. The disadvantages of apomorphine test include the possible placebo effect and potentially subjective scoring by the investigators and the different criteria for interpreting test results. Side effects from apomorphine (nauses, vomiting, sedation, and hypotension) are not tolerable by some patients and thus preclude the evaluation. $^{123}$I-IBZM is a dopamine D2 receptor antagonist detectable by SPECT. Both in vitro and in vivo evaluations have shown that $^{123}$I-IBZM bind specifically to striatal D2 receptor [4-8]. The radiation dosimetry and pharmacology data suggest that $^{123}$I-IBZM is safe for human use [7]. $^{123}$I-IBZM SPECT provides a more objective measurement than apomorphine test. A strong correlation between clinical response to apomorphine and D2 receptor status as demonstrated by $^{123}$I-IBZM SPECT has been reported [3,9,10]. Intraindividual comparison in patients with parkinsonism proves that binding of ligands to dopamine D2 receptors assessed by $^{11}$C-raclopride positron emission tomography (PET) is reflected by readily available $^{123}$I-IBZM SPECT [11]. Imaging of dopamine D2 receptors with $^{123}$I-IBZM SPECT appears to distinguish between patients with de novo parkinsonism that is levodopa-responsive (probably Parkinson’s disease of Lewy body type) and that which does not respond to levodopa therapy [10,12].

Motor fluctuation, dyskinesia, neuropsychiatric complications and autonomic
dysfunction are major disabling problems of late idiopathic PD. Previous studies with either $^{123}$I-IBZM SPECT [13-15] or $^{11}$C-raclopride PET [16] have shown downregulation of striatal dopamine D2 receptor binding in chronic PD with motor fluctuation. We intend to compare the D2 receptor status among de novo untreated PD, chronic PD with stable response to levodopa, and chronic PD with motor fluctuation and dyskinesia and try to elucidate the pathophysiology of fluctuating drug response in late PD patients. Besides, the extrastriatal D2 receptor status will be evaluated and correlated with neuropsychiatric complications and autonomic dysfunction.

The aims of our study were:

1. Discrimination between idiopathic Parkinson’s disease (PD) and “Parkinsonism-plus” syndromes is important because of differences in response to treatment and prognosis. Besides, the enrollment of correctly diagnosed PD patients are important for analytical epidemiological study and clinical trials of new medicine. The first objective is to use the dopamine D2 receptor ligand-iodobenzamide (IBZM) to define the sensitivity and specificity of $^{123}$I-IBZM SPECT for discriminating between PD and “Parkinsonism-plus” syndromes.

2. Motor fluctuation and dyskinesia are two major disabling problems of late PD. Previous studies with either $^{123}$I-IBZM SPECT or $^{11}$C-raclopride PET have shown downregulation of striatal dopamine D2 receptor binding in chronic PD with motor fluctuation. The second objective of this study is to compare the D2 status among de novo untreated PD, chronic PD with stable response to levodopa, and chronic PD with motor fluctuation and dyskinesia, and try to elucidate the pathophysiology of fluctuating drug response in late PD patients.

二、研究方法與過程

Setting: ambulatory or hospitalized patients in a both primary and referred care center
Design: cross-sectional study
Participants:
- group I: 6 controls---age-matched healthy subjects or patients with no known impairment of dopamine homeostasis (eg, muscle contraction headache).
- group II: 5 de novo untreated PD patients (disease duration < 1 year)
- group III: 13 chronic PD patients with stable response to levodopa
- group IV: 10 PD patients with motor fluctuation and dyskinesia
- group V: 6 “parkinsonism-plus” syndrome patients
  (multiple system atrophy, progressive supranuclear palsy)

The inclusion diagnostic criteria of PD were: 1) the presence of at least two of the following signs: rest tremor, rigidity, bradykinesia, and postural reflex impairment; at least one of which must be either rest tremor or bradykinesia; 2) parkinsonism could not be caused by trauma, brain tumor, infection, cerebrovascular disease, other known neurological disease or by known drugs, chemicals, or toxins; 3) absence of prominent oculomotor palsy, cerebellar signs or amyotrophy; and 4) improvement with levodopa therapy [17].
The identification of “parkinsonism-plus” syndrome is based on the presence of parkinsonian features, no or only transient response to dopaminergic medications, and the appearance of any clinical signs not compatible with PD, such as cerebellar signs, pyramidal tract signs, severe autonomic dysfunction, vertical down-gaze palsy, or an alien hand. Patients with secondary causes of parkinsonian syndrome, such as stroke or CO intoxication will be excluded from this group.

procedures:

Preparation

Informed consent was obtained from each participant. Every subject received a brain magnetic resonance imaging (MRI, 1.5 tesla) and $^{123}$I-IBZM SPECT study. Patients are premedicated with oral Lugol’s solution (3ml each dose, totally 3 doses) to protect thyroid gland. Previous study has shown that $^{123}$I-IBZM binding in D2 receptor is reduced by dopamine agonists but not levodopa [18]. Patients who are taking dopamine agonists are withdrawn from the drugs for 2 days prior to the $^{123}$I-IBZM SPECT investigation. Patients suffered from severe rest tremor or dyskinesia and had the potential for seriously degrading image quality were given midazolam 15 mg 30 min before MRI and $^{123}$I-IBZM SPECT study.

SPECT Image Acquisition

IBZM binding was assessed by SPECT 2 h after intravenous injection of 185 MBq (4.8 mCi) $^{123}$I-IBZM (核能研究所, Taiwan, R.O.C.). A rotating three-headed gamma camera with 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 ($360^\circ$ rotation) in a 128 x 128 matrix. The acquisition time was 50 seconds per projection. Transverse images were reconstructed by filtered backprojection (Butterworth filter) with a subsequent computation of coronal slices (slice thickness 6.0 mm). Attenuation correction was performed in selected transverse slices according to a modified Chang’s method [19].IN-plane resolution of the reconstructed images is 8.5 mm FWHM, and slice thickness is approximately 6 mm.

MRI Image

T-1 weighted MRI images with thin cuts focused on basal ganglia are obtained on the same day in axial planes on a Magneton 1.5 Tesla scanner (Siemens, Iselin, NJ).

SPECT Data Analysis

1. For semiquantitative evaluation of specific tracer uptake, regions of interest (ROIs) were drawn manually over 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 activity (BG/FC) was calculated. Values of left and right hemisphere ROIs were combined.
2. A more sophisticated method for SPECT data analysis is designed using SPECT and MRI registration. (NCS87-2218-E006-065).

Statistical methods:
For determining the sensitivity and specificity of $^{123}$I-IBZM SPECT in discrimination between idiopathic PD and “parkinsonism-plus” syndromes, the result of $^{123}$I-IBZM SPECT were considered abnormal if the BG/FC ratio was less than mean minus 2 SD of controls. The data from groups II and that from group V would be used to determine the sensitivity and specificity of $^{123}$I-IBZM SPECT.

(2) For the second objective, ANOVA is used for inter-group comparisons (groups II-IV). When p value of Kruskal-Wallis test <0.05, then use Dunns multiple comparison test to calculate.

Table 1 summarizes the demographic data, Hoehn and Yahr stage, duration of illness, and basal ganglia/frontal cortex (BG/FC) ratio in normal controls (Group I), idiopathic PD patients of variable levodopa response stages (Groups II-IV), and patients with “parkinsonism-plus” syndromes (Group V). Unfortunately, 3 of 6 controls and 1 patient in group V received $^{123}$I-IBZM SPECT on the same day were later found to have poor $^{123}$I-IBZM binding. The data were discarded. We will continue our studies for more normal controls in the near future. The illustrations of basal ganglion uptake of I-123-IBZM in idiopathic Parkinson’s disease with variable levodopa response (Group II-IV), and in “parkinsonism-plus” syndromes (Group V) were should in Figure 1.

Previous studies with $^{123}$I-IBZM SPECT had shown no significant difference in BG/FC ratio between normal controls and early stage PD patients. However, $^{11}$C-raclopride PET study showed increased D2 receptor densities in early stage PD patients than in controls. Either $^{123}$I-IBZM SPECT or $^{11}$C-raclopride PET study confirms the notation that idiopathic PD is a presynaptic disorder, and the D2 receptor densities are normal or even increased in the early stage. Inference from previous reports can be made that $^{123}$I-IBZM SPECT cannot tell early stage PD from normal controls, while $^{11}$C-raclopride PET study can differentiate these two group subjects. It means that $^{11}$C-raclopride PET is superior to $^{123}$I-IBZM SPECT in the diagnosis and identification of early stage PD.

A comparison among Groups II-IV showed that PD with motor fluctuation and dyskinesia had decreased D2 receptor densities than de novo untreated or stable response PD patients. This may be a result of structural adaptation of the postsynaptic dopaminergic system to the progressive decline of nigrostriatal neurons. This finding can be used to explain the unpredictable “on-off” or “freezing” phenomenon in advanced PD patients. The inhibitory postsynaptic potential is a function of the quantal content, quantal size, and D2 receptor response. In more advanced PD, the dopamine release decreased. The presynaptic reduction of dopamine release and reduced postsynaptic D2 receptor densities resulted in a fall in amplitude of the inhibitory postsynaptic potential, which may be insufficient to depolarize striatal neurons to threshold. The combination of both presynaptic and postsynaptic defects resulted in a diminished “safety factor”, which made some neurons fail to fire successfully. This is the most likely cause of the sudden switch of motor performance in advanced PD patients.

Our data on 5 “parkinsonism-plus” syndrome patients showed nonsignificantly mildly decreased mean values of BG/FC ratio from those of de novo untreated
patients and stable responders of PD. There are some overlaps of BG/FC ratio between idiopathic PD and “parkinsonism-plus” syndrome patients. Previous studies had shown a reduction of BG/FC ratio in “parkinsonism-plus” syndrome patients (10,12,19). The discriminative ability of $^{123}$I-IBZM SPECT between idiopathic PD and “parkinsonism-plus” syndromes must be judged carefully. Previous studies on “parkinsonism-plus” patients usually did not specify the duration of illness and timing of the study. Our study and previous reports showed a progressive decline in BG/FC ratio in advanced PD patients. A single random $^{123}$I-IBZM SPECT study must be interpreted carefully, considering the natural decline in PD patients and some overlaps between PD and “parkinsonism-plus” syndromes. For clarifying the differentiating ability of $^{123}$I-IBZM SPECT between idiopathic PD and “parkinsonism-plus” syndromes, enrollment of patients at early stage, and follow-up of clinical symptoms/signs, drug response, and MRI, $^{123}$I-IBZM SPECT study longitudinally may be used to answer the above question. The differentiation is more significant at an early stage in terms of clinical trials, analytical epidemiological study, and genetic study. We will continue the studies on “parkinsonism-plus” patients.

Table 2 summarizes 10 patients with unilateral PD. The BG/FC ratio was found to be increased contralaterally to the symptoms in 2 cases, and ipsilaterally in 8 cases. Previous studies on unilateral PD found contralateral upregulation of D2 receptor density, but there were also few cases with ipsilateral upregulation. Previous reports had shown no significant difference in combined bilateral BG/FC ratio between normal controls and early stage PD patients. The findings of asymmetric BG/FC ratio in PD patients may thus imply a minimal or mild downregulation of D2 receptor densities on predominantly ipsilateral side, thus made the mean values no difference. The hemiparkinsonian symptoms possibly are not caused exclusively by unilateral damage of the nigrostriatal pathway, but the patients may also have nigrostriatal damage on the ipsilateral side.

$^{123}$I-IBZM SPECT is useful in differentiating among various parkinosian syndromes and it may help to predict the dopaminergic response. Moreover, visualizing the D2 receptor can also be used to enroll homogeneous patient population for clinical trials, studying both experimental pharmacological and surgical therapies.

Interestingly, we found a high percentage of extrastriatal uptake of I-123 IBZM in the thalamus (60%), midbrain (40%), Mesial temporal (78%), prefrontal (12%), cingulate gyrus (72%), and pituitary gland (23%), which should no significant difference between groups and between right or lift side. (Fig 2)

The extrastriatal uptake percentage is much higher than in previous reports. These findings may suggest that I-123 IBZM provided by INER has a high affinity to D2-receptor sites so that those extrastriatal areas with low D2-receptor density can still be detected in this study. The high extrastriatal uptake may facilitate the use of I-123 IBZM in the assessment of psychiatric disorders.

四、參考文獻


Table 1. The demographic data, Hoehn and Yahr stage, duration of illness, and basal ganglia/frontal cortex ratio in normal controls (Group I), idiopathic Parkinson’s disease patients of variable levodopa response stages (Groups II-IV), and patients with “Parkinsonism-plus” syndromes (Group V)

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
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<tr>
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<td>13</td>
<td>9</td>
<td>6</td>
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<td>M:F</td>
<td>2:1</td>
<td>3:2</td>
<td>7:6</td>
<td>8:1</td>
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<td>Age(yr)</td>
<td>66.0±5.0</td>
<td>61.8±13.7</td>
<td>64.4±7.5</td>
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<td></td>
<td>(61-71)</td>
<td>(47-75)</td>
<td>(51-75)</td>
<td>(40-74)</td>
<td>(65-81)</td>
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<td>BG/FC</td>
<td>1.67±0.03</td>
<td>1.71±0.10</td>
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<td>(1.63-1.73)</td>
<td>(1.57-1.84)</td>
<td>(1.53-1.94)</td>
<td>(1.34-1.82)</td>
<td>(1.55-2.02)</td>
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<td>Hoehn &amp; Yahr Stage</td>
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<td>(3-4)</td>
<td>(3-5)</td>
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<td>Duration of illness(yr)</td>
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<td>(5.4-13.3)</td>
<td>(2.5-7.0)</td>
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<td>Contralateral side</td>
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Table 2. The basal ganglia/frontal cortex ratio of unilateral Parkinson's disease patients
(Group II: cases 1-5, Group III: cases 6-10)
Figure 1

Illustrations of basal ganglion uptake of I-123-IBZM in idiopathic Parkinson’s disease with variable levodopa response (Group II-IV), and in “parkinsonism-plus” syndromes (Group V).

Group II

Group III

Group IV

Group V
Figure 2

Extrastriatal uptake of I-123 IBZM in Thalamus, Midbrain, Mesial temporal, pituitary gland, Cingulate gyrus, and Prefrontal area.

Thalamus
Midbrain
Mesial temporal

Pituitary gland
Cingulate gyrus
Prefrontal area.