Technetium-99m-HMPAO Brain SPECT in Behçet's Disease

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Behçet's disease (BD) is an idiopathic multisystem disorder. Involvement of the central nervous system (CNS) occurs in 4%–48% of cases. The aim of this study was to evaluate ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) SPECT findings in BD patients and eventually to detect CNS involvement by depicting cerebral blood flow disturbances. **Methods:** Technetium-99m-HMPAO brain SPECT was performed on 33 consecutive BD patients. Qualitative and quantitative evaluation of the cortical uptake was done using an automatic program that generated 32 regions of interest (ROIs). An uptake index for each ROI was obtained. Reference values were obtained from a healthy control group (n = 20). Twenty-five patients also had an MRI study. **Results:** Twelve of 32 patients (36%) presented with a clinical neurological disorder. SPECT and visual evaluation revealed that 17 patients (51.5%) had abnormalities; 9 of 25 MRI studies (36%) were abnormal. Using the quantitative approach for SPECT, 23 patients (69.7%) had abnormally low values. Six of 12 patients with neurological symptoms had a visually abnormal SPECT scan, whereas quantitative analysis showed abnormalities in 11 patients. Of the 21 patients with no neurological findings, 9 had abnormal SPECT results, and 12 had low uptake indexes. **Conclusion:** HMPAO brain SPECT shows high rates of cerebral blood flow abnormalities in BD patients presenting with neuropsychiatric symptoms, and it also is frequently abnormal in asymptomatic BD patients who have no abnormalities on MR scans. Compared with visual analysis, quantitative analysis detects an even higher rate of SPECT changes in BD patients.

Key Words: Behçet's disease; SPECT; regional cerebral blood flow; technetium-99m-hexamethyl propyleneamine oxime

J Nucl Med 1998; 39:950–954

Behçet's disease (BD) (*1–4*) was originally described by Hulûsi Behçet, a Turkish dermatologist, as a trisyndrome of recurrent outbreaks of aphthous ulcerations of the mouth, genitalia and iritis, often leading to blindness. At least 70% of patients have other clinical manifestations such as phlebitic phenomena, skin lesions, arthritis, synovitis, digestive system disturbances, artery aneurysms and neurological involvement, among others. Not all patients present with the expected triad. In 1990, the International Study Group for Behçet's Disease (*4*) established a set of unified international diagnostic criteria, namely, mouth aphthae associated with two of the following manifestations: aphthae in the genitalia, typical eye lesions, typical skin lesions or a positive pathergia test. Behçet's disease leads to occasional serious complications, mainly neurological involvement and ulcerative intestinal disease. The etiology remains unknown. Among the different etiological hypotheses put forward, the infectious, coagulopathic, genetic and autoimmune hypotheses are outlined. The highest prevalence occurs in Japan, where BD is a frequent cause of blindness. It also is common in the Mediterranean countries. The pathological hallmark is vasculitis of small vessels with lymphomonocytic perivascular infiltration and an exaggerated chemotactic response of polymorphonuclear cells. The frequency of neurological involvement ranges from 4% to 48% of cases according to previous reports (*5–8*).

Because neurological complications are a major cause of morbidity and mortality in BD, and because there is a lack of reliable laboratory tests to detect CNS involvement (which may be reverted by immunosuppressive therapy), there is a clear need for a method that can depict such involvement, even at an early subclinical stage. Given this background, we undertook this study to describe potential brain SPECT abnormalities in BD patients.

MATERIALS AND METHODS

All patients attending our internal medicine service during 24 consecutive months who satisfied the criteria for diagnosis of BD participated in the study.

We studied 33 BD patients (15 women, 18 men; age range 18–69 yr); mean age 44.5 yr). Twelve patients presented with neurological manifestations (36%) (Table 1), and 21 presented without neurological symptoms.

Twenty control subjects also participated in our study (10 women, 10 men; age range 23–60 yr; mean age 43 yr). We followed our committee's ethical guidelines and obtained informed consent from all participants. There were no significant differences between the patients' and control group's ages.

Study Protocol

A ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) brain SPECT study was performed on all patients and control subjects. MRI also was performed on 25 patients. A 1.0-T unit (Siemens Medical Systems, Iselin, NJ) was used to acquire a standard set of images. The study included axial T1 and T2 spin-echo sequences.

Brain SPECT

Brain SPECT was performed 10 min after intravenous injection of 740 MBq ^{99m}Tc-HMPAO (Ceretec, Amersham, Buckinghamshire, England) using a rotating, single-head gamma camera (Elscint SP4-HR, Haifa, Israel) equipped with a high-resolution, parallel-hole collimator. Data were acquired in a 64 × 64 matrix through 360° rotation at 3° intervals for 15 sec per view. Our acquired pixel size was 0.4587 cm/pixel. The average radius of rotation was 15 cm. Approximately 5–6 million counts were acquired per patient. Data reconstruction of transaxial slices was performed by filtered backprojection. We used a Metz filter for this tomographic reconstruction (power 3.000, FWHM 14 mm, cutoff 31). The reconstructed pixel size was the same as the acquired one. Attenuation correction was not performed.

Visual interpretation of the cortical uptake was done by two experienced nuclear medicine physicians who had no clinical information. Attention was paid to the presence of any brain perfusion abnormality.

Quantitative evaluation of the cortical uptake also was performed by applying preformed templates on four transaxial slices

Received Feb. 1, 1997; revision accepted Sep. 27, 1997.
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TABLE 1
Neurological Features of 12 Symptomatic Patients

Patient no.	Symptom
6	Confusional symptoms, cephalalgia, transient ischemic attack
7	Cephalalgia
9	Cephalalgia, neurosensorial hypoacusia, VII cranial nerve palsy
11	Cephalalgia, depression
12	Neurosensorial hypoacusia, migraine
15	Myelomeningoencephalitis, aseptic meningitis
18	Benign endocranial hypertension (BEH)
24	BEH
26	Meningo encephalitis, aseptic meningitis
27	Stroke
30	BEH
33	Meningoencephalitis, stroke, aseptic meningitis

over the orbitomeatal line (OML) at approximately 3, 5, 6 and 8 cm. The slice thickness used for the quantitation was 1 cm. These templates were based on a brain atlas (*9*) delineating anatomic structures at the different slice levels. A semiautomatic program generated 32 regions of interest (ROIs) in the four templates (Fig. 1). The size of each template could be manually adjusted, so that its contour fit any brain surface well. The size of the 32 ROIs within the template was relative to the dimensions of each template. An uptake index was derived using the ratio between the mean counting rate within the ROI and the mean counting rate for all the ROIs in the same slice. Reference values were obtained from the healthy control group (95% confidence interval of the mean) (Table 2). Regions with an uptake index outside the reference limits were considered abnormal.

RESULTS

Brain SPECT

Control group. None of the control subjects had visually apparent cortical abnormalities or uptake values within normal limits. Table 2 shows normal values for each of the 32 regions.

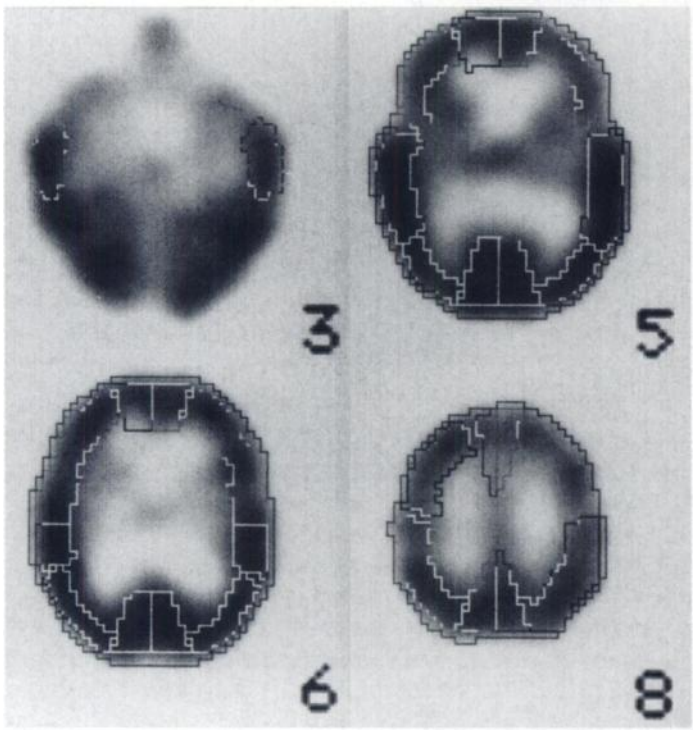

FIGURE 1. Regions of interest in four brain transaxial slices 3, 5, 6 and 8 cm above the orbitomeatal line.

TABLE 2
Normal Regional Uptake Values (95% Confidence Interval for the Mean)

Area	Left	Right
Temporal (Slice 3)	0.779–0.951	0.778–1.011
Temporal (Slice 5)	0.972–1.004	0.991–1.027
Temporal (Slice 6)	0.996–1.034	1.009–1.045
Frontal 1 (Slice 5)	0.983–1.022	0.970–1.023
Frontal 2 (Slice 5)	0.952–0.994	0.960–0.992
Frontal 1 (Slice 6)	0.959–1.002	0.963–1.011
Frontal 2 (Slice 6)	0.954–0.980	0.949–0.974
Frontal 1 (Slice 8)	0.848–0.909	0.876–0.947
Frontal 2 (Slice 8)	0.947–1.010	0.966–1.016
Occipital 1 (Slice 5)	0.927–0.967	0.940–0.983
Occipital 2 (Slice 5)	1.068–1.115	1.035–1.084
Occipital 1 (Slice 6)	0.941–0.985	0.968–1.002
Occipital 2 (Slice 6)	1.053–1.091	1.018–1.067
Parietal 1 (Slice 8)	1.014–1.066	1.056–1.120
Parietal 2 (Slice 8)	1.050–1.117	1.009–1.069
Basal ganglia	0.893–0.956	0.923–0.986

Patients. Visual evaluation revealed cortical defects in 51.5% of the patients (Fig. 2). Some of the patients had several perfusion abnormalities. These were located in the following areas: 10 frontal (48%), 6 occipital (28%) and 5 temporal (24%). No significant perfusion defects were observed in the remaining 16 patients (Table 3).

Quantitative analysis detected abnormally low values in 69.7% of the patients: 12 frontal (44%), 8 occipital (30%), 7 temporal (26%). 10 patients did not show abnormal values.

MRI findings were abnormal in 9 patients (36%) and normal in 16.

SPECT and MRI findings were normal in 10 subjects and abnormal in 6. In 9 patients, abnormalities were found only in either one of the two studies (6 SPECT and 3 MRI).

Of the 3 patients with abnormal MRI and normal SPECT results, MRI findings were as follows: 1 with multiple, probably ischemic, lesions within the white matter; 1 with an ischemic lesion in the left putamen and 1 with small lesions in the

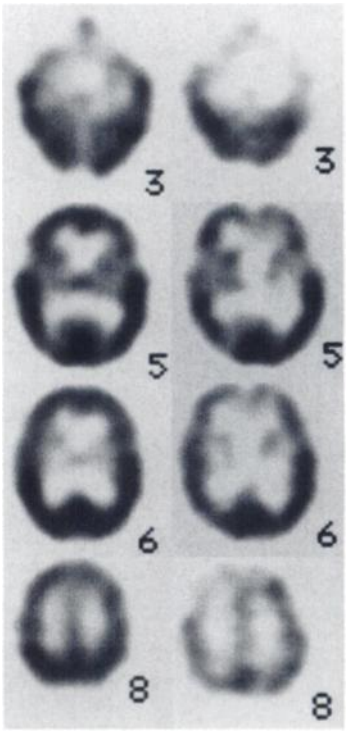

FIGURE 2. Transaxial slices from 3, 5, 6 and 8 cm of the orbitomeatal line of a control subject (left). The same slices from Patient 28 are shown on the right.

TABLE 3
Visual and Quantitative SPECT and MRI Findings from 33 Behçet's Disease Patients (12 Symptomatic and 21 Asymptomatic)

Patient no.	Symptoms	MRI	Visual analysis SPECT	Quantitative analysis
1	No	—		Normal
2	No	Normal	Right frontal defect	Right frontal decreased uptake
3	No	Normal	Normal	Normal
4	No	—	Normal	Normal
5	No	Normal	Normal	Right occipital decreased uptake
6	Yes	Multiple lesions in the white matter	Normal	Bilateral frontal decreased uptake
7	Yes	Normal	Left temporal defect	Left temporal decreased uptake
8	No	Normal	Normal	Bilateral frontal decreased uptake
9	Yes	Multiple lesions in the white matter	Left frontal defect	Bilateral frontal and right basal ganglia decreased uptakes
10	No	Bilateral subinsular lesions	Normal	Normal
11	Yes	Normal	Normal	Right temporal decreased uptake
12	Yes	Left frontal lesion	Left frontal defect	Left frontal decreased uptake
13	No	—	Right frontal defect	Bilateral frontal decreased uptake
14	No	—	Normal	Normal
15	Yes	Protuberantial lesion	Left occipital and left frontal defects	Bilateral occipital, left frontal and basal ganglia decreased uptakes
16	No	—	Left occipital defect	Left occipital decreased uptake
17	No	Normal	Left temporal defect	Left temporal decreased uptake
18	Yes	Normal	Bilateral occipital defects	Bilateral occipital decreased uptake
19	No	Normal	Left occipital defect	Left occipital defect decreased uptake
20	No	Normal	Bilateral frontal defects	Bilateral frontal decreased uptake
21	No	Normal	Normal	Right basal ganglia decreased uptake
22	No	Chronic infarct in left PCA	Left temporal and left occipital defects	Left temporal and left occipital decreased uptake
23	No	Left putamen lesion	Normal	Normal
24	Yes	Normal	Left frontal defect	Left frontal and left occipital decreased uptake
25	No	Normal	Normal	Normal
26	Yes	Normal	Normal	Bilateral temporal decreased uptake
27	Yes	Multiple lesions in the white matter	Right frontal defect	Right frontal decreased uptake
28	No	Multiple lesions in the white matter	Right frontal and left temporal defects	Bilateral frontal and left temporal decreased uptake
29	No	Normal	Left frontal and left temporal defects	Left frontal and left temporal decreased uptake
30	Yes	Normal	Normal	Normal
31	No	Normal	Normal	Normal
32	No	—	Normal	Normal
33	Yes	—	Bilateral occipital defect	Bilateral occipital decreased uptake

PCA = posterior cerebral artery; — = no data.

subinsular white matter bilaterally. Quantitative SPECT analysis was abnormal in the first patient.

Table 4 shows the correlations between diagnostic procedures and symptoms. There was a high incidence of SPECT abnormalities in patients with and without CNS clinical manifestations. Using the quantitative approach, the rate of abnormal findings increased from 51.5% to 69.7%. No relationship was observed between the duration of disease from the time of diagnosis and the SPECT findings.

TABLE 4
Visual and Quantitative SPECT and MRI Evaluations According to the Presence of Neurological Clinical Manifestations

	Visual SPECT		Quantitative SPECT		MRI	
Group	N	A	N	A	N	A
Asymptomatic	12	9	9	12	10	4
Symptomatic	4	8	1	11	6	5

N = normal; A = abnormal.

A Mann-Whitney U-test was used to compare the mean uptake values for control subjects and BD patients in each of the 32 regions. Significant differences were found in 7 regions: (a) In a slice 3 cm over the OML, no significant differences were found; (b) in a slice 5 cm over the OML, significant differences were found in left frontal area 1 ($p = 0.0427$); (c) in a slice 6 cm over the OML, significant differences were found in the left occipital 1 ($p = 0.01$) and right occipital 1 ($p = 0.02$) and (d) in a slice 8 cm over the OML, significant differences were found in the left frontal 1 ($p = 0.0002$), right frontal 1 ($p = 0.0055$), right frontal 2 ($p = 0.0121$) and right parietal 1 ($p = 0.0011$).

DISCUSSION

Of the patients with BD (*5–8*), 4%–48% have neurological involvement related to the systemic phase of the disease, which is associated with the presence of aphthae and with other systemic manifestations occurring months or years after onset, although in 5% of the patients CNS disease is the initial feature (*5*). In 30% of these cases, the initial neurological manifestations slowly progress by days or weeks, and in 70%, the initial

TABLE 5
Neurological Symptoms in Behçet's Disease

1. Cephalalgia
2. Meningoencephalitis
3. Recurrent aseptic meningitis or isolated encephalitis
4. Benign endocranial hypertension
5. Ataxia and cerebellar signs
6. Oculomotor or other cranial nerve palsies
7. Speech disorders (disartria, aphasia)
8. Transient ischemic attacks and stroke
9. Bulbar and pseudobulbar paralysis
10. Spinal cord disorders
11. Multiple sclerosislike syndromes
12. Pyramidal and extrapyramidal involvement
13. Psychiatric alterations such as psychosis
14. Neuritis and polyneuritis
15. Dementia
16. Seizures
17. Confusion
18. Loss of vision, diplopia and nystagmus

The neurological and psychiatric manifestations are nonspecific and include the following list. Any level of the nervous system may have diffuse or focal involvement. TIAs = transient ischemic attacks.

stage is acute, with periods of remission, during which the patient may be asymptomatic or show permanent neurological damage (*10*).

Symptoms may vary (Table 5), probably because any part of the central or the peripheric nervous system may be involved (brain stem, spinal cord, basal nuclei, cerebral hemispheres and cerebellum), either with focal or diffuse lesions.

Although neurological lesions in BD have a poor vital and functional prognosis (*5*), recent studies are more optimistic in that respect. However, they are among the most severe manifestations of the disease. Compared with the older series, today neuro-Behçet mortality has decreased from 21%–41% (*5*) to 5%–12% (*6,7*), but its prognosis is still uncertain.

Pathophysiology in neuro-Behçet remains unclear. Different hypotheses include: vasculopathy; chemical mediators that cause brain damage such as interleukin 6, Oligoclonal Ig A and Ig M bands; anticardiolipine antibodies. These may cause ischemia or demyelinization. Pathology shows vasculitis involving small vessels with perivascular meningoinfiltration of lymphocytes, thickening and thrombosis of arteries and small veins and necroinfarcted areas scattered through the brain, mainly across the subcortical white matter.

Several studies have reported the use of MRI and CT in patients with BD (*11–24*). Although CT scans may be strictly normal or show nonspecific findings, MRI is more sensitive to picking up encephalitic lesions and usually correlates better with neurological examination. The most frequent locations for MRI lesions are in the brain stem and the cerebral white matter. Other locations include the basal ganglia, cerebellum, thalamus, cerebral hemispheres, optic nerves and spinal cord. White-matter lesions are usually small and asymptomatic, whereas brain stem lesions are extensive and symptomatic. Moreover, immunosuppressive treatment may result in improvement of both MRI lesions and symptoms.

There have been a few studies using PET (*25–27*). Abnormal glucose metabolism and decreased cerebral blood flow measured have been described. Use of SPECT in BD patients has been reported only occasionally. Watanabe et al. (*28*) studied a BD patient using SPECT and found cortical defects in the right frontal, parietal, temporal and occipital lobes, whereas MRI detected lesions only in white matter. Mizukami et al. (*29*) compared the neurological involvement of three neuro-Behçet patients using CT, MRI and brain SPECT. Park-Matsumoto et al. (*30*) found bilateral frontal hypoperfusion in one patient. Using ^{123}I-IMP, Matsuda et al. (*31*) found bilaterally decreased cortical perfusion in the cerebellar hemispheres in one patient. Terao et al. (*32*) studied one patient using SPECT and found increased perfusion in the left motor cortex and in the ipsilateral thalamus. Finally, Arai et al. (*33*) found a marked reduction of blood flow in the frontal cortex of one BD patient with dementia and personality changes.

In our study, HMPAO brain SPECT frequently was found to be abnormal in BD patients who presented with neuropsychiatric symptoms; however, SPECT also was often abnormal in asymptomatic patients. The high prevalence of SPECT abnormalities in asymptomatic patients, together with the lack of a correlation with MRI structural abnormalities, suggests a primary blood flow deficit or a local metabolic disturbance (*34*), probably expressing early, subclinical CNS involvement. Using inspective analysis, we found that the most common localization of defects was in the frontal lobe, occurring in 48% of cases. Using quantitative evaluation, we found that the percentage of abnormal findings increased from 51.5% to 69.7%.

According to Akman-Demir's (*35*) 7-yr follow-up study, silent neurological involvement may occur in BD, and patients should undergo periodic neurological evaluation. Although MRI may reveal morphological abnormalities in many patients, predominantly in the white matter, it should be helpful to identify changes before structural damage occurs. In our experience, functional neuroimaging with SPECT may display brain perfusion defects at an early stage. Although MRI is a useful method for detecting neuro-Behçet lesions of the CNS, SPECT is suitable for a better understanding of the hemocirculatory and metabolic features of the illness as well as for monitoring the patient's clinical condition and treatment response. It is evident that CNS involvement in BD must be diagnosed precociously, and a method such as cerebral SPECT aims at that.

CONCLUSION

There is a high prevalence of cerebral perfusion damage in BD patients, and quantitative evaluation detects even higher rates of abnormalities. Such defects are found mainly in symptomatic patients, but they also are found frequently in asymptomatic patients. Thus, brain perfusion SPECT is a sensitive and feasible method for detecting CNS involvement in BD patients and may be of considerable diagnostic value, especially early in the course of disease, when it may detect subclinical neurological involvement. Furthermore, with the addition of quantitative analysis, SPECT could play a role in the management of BD patients with early CNS involvement, perhaps also providing an objective measurement of the efficacy of therapy.

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Loss of Dopamine-D2 Receptor Binding Sites in Parkinsonian Plus Syndromes

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This study analyzed temporal changes of striatal dopamine-D2 receptor binding during the course of different extrapyramidal movement disorders using ^{123}I-iodobenzamide (IBZM) SPECT. **Methods:** Eighteen patients (9 with Parkinson's disease, 9 with parkinsonian plus syndrome) were followed for 11–53 mo. Dopamine-D2 receptor binding was assessed using ^{123}I-IBZM SPECT at the beginning and at the end of the follow-up period. SPECT data were acquired 120 min postinjection of 3–5 mCi ^{123}I-IBZM. A semiautomated algorithm was applied to the raw data for semiquantitative evaluation of regional cerebral receptor binding. **Results:** Intraobserver ($r = 0.992$) and interobserver ($r = 0.930$) variance was low for the semiautomated interpretation of the SPECT examination of the dopaminergic D2 receptor binding, reflecting a highly reproducible SPECT algorithm. Mean specific dopamine-D2 receptor binding was lower in patients with parkinsonian plus syndrome compared to patients with Parkinson's disease on the initial ($p < 0.001$) as well as the follow-up study ($p < 0.001$). In patients with Parkinson's disease, we observed an unaffected receptor binding compared to a reduced binding of radiotracer in patients with parkinsonian plus syndrome during the course of the disease ($p < 0.001$). **Conclusion:** During the follow-up, patients with Parkinson's disease showed a constant dopamine-D2 receptor binding. In contrast, patients with parkinsonian plus syndrome revealed a decline of the binding of dopamine-D2 receptor. These findings are in agreement with histopathological data that demonstrated a preserved dopamine-D2 receptor status in patients with Parkinson's disease and a decline of the dopamine-D2 receptors in patients with parkinsonian plus syndrome. SPECT examinations using ^{123}I-IBZM are useful for assessing dynamic changes of dopamine-D2 receptors in extrapyramidal movement disorders. Semiquantitative SPECT evaluations may provide valuable information for clinical management and prognosis of the patient with extrapyramidal movement disorders.

Key Words: Parkinson's disease; parkinsonian plus syndromes; iodine-123-iodobenzamide; SPECT

J Nucl Med 1998; 39:954–960

Parkinson's disease, multiple system atrophy and progressive supranuclear palsy are pathologic conditions that involve the extrapyramidal control of voluntary and involuntary movement. It is well known that these conditions are difficult to discriminate by clinical means although the underlying pathology is distinct. In fact, even in specialized centers, in up to 30% of the cases clinically diagnosed as Parkinson's disease, postmortem examination revealed changes consistent with multiple system atrophy or other parkinsonian disorders (*1,2*). Although some encouraging results have been published recently using MRI (*3,4*), structural neuroimaging fails to identify, with sufficiently high specificity, these different extrapyramidal disorders. Since the prognosis varies among these disorders, being rather poor in patients with parkinsonian plus syndrome compared to patients with Parkinson's disease, active diagnostic information is use-

Received Feb. 1, 1997; accepted Sept. 4, 1997.

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