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Dopamine Transporter Imaging for Distinguishing Between Idiopathic Parkinson's Disease and Secondary Parkinsonism

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1. Introduction

Idiopathic Parkinson's disease (IPD), first described by James Parkinson in 1817, is a sporadic neurodegenerative disorder. The main clinical features include masked face, resting tremor, bradykinesia, rigidity, festinating gait, and loss of postural reflexes. The clinical features are most insidious and usually asymmetric at onset. The asymmetry may persist even in a late stage and progress slowly. The pathological findings are characterized by loss of pigmented dopamine neurons in the substantia nigra, particularly the pars compacta and locus ceruleus, and the presence of Lewy bodies. The cause of IPD remains unknown.

Parkinsonism (PM) is not a single disease but a common clinical presentation. The clinical syndrome is characterized by tremors, bradykinesia, rigidity, and postural instability. Exposure to toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which was sold as "synthetic heroin," manganese (Mn), carbon disulfide (CS_2), carbon monoxide (CO), methanol, cyanide, and other organic solvents may cause brain damage, leading to features similar to PM. Many neurodegenerative disorders may present with PM, including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), spinocerebellar atrophy (SCA), and corticobasal sundrome (CBS). Several genetic diseases, including dopa-responsive dystonia (DRD), Wilson's disease (WD), and Huntington's disease (HD), may cause degeneration in the basal ganglia or affect the dopaminergic pathway. Furthermore, some dementia syndromes may be associated with PM, including vascular parkinsonism (multiple infarct parkinsonism), dementia with Lewy bodies (DLB), and frontotemporal dementia, and parkinsonism linked to chromosome 17 (FTD-17).

The main treatment of IPD includes the use of dopamine, dopamine agonists, monoamine oxidase inhibitors, and catechol-*o*-methyltransferase inhibitors. The above medications are

usually effective in IPD patients, whereas their effects are usually limited in patients with secondary parkinsonism. Although definite diagnosis of IPD is based on typical pathological findings, early diagnosis is very important as it leads to early treatment.

IPD and PM are distinguished on the basis of the onset of symptoms, symmetry of clinical features, characteristics of tremors, rigidity, bradykinesia, and other associated symptoms, such as cognitive impairment, limitation of eye ball movement, ataxia, and autonomic dysfunction. In addition, information concerning family history, smoking and alcohol exposure, diabetes with hypertension, and exposure to toxic substances are also essential for diagnosis. Despite differences in the clinical features of IPD and PM, definite diagnosis may be difficult; therefore, reliable imaging is helpful for early and accurate diagnosis.

2. Dopamine transporter (DAT) scan

Dopamine transport is one of the primary mechanisms that can modulate the dopaminergic tone via an active transport system that involves the re-uptake of dopamine. Cocaine analogues including (1r) 2β-carbomethoxy-3β-(4-iodophenyl) tropane (β-CIT), and ^{123}I-FP-CIT have been developed as single photon emission computed tomography (SPECT) imaging agents. Both agents can bind at the DAT site of dopamine neuron terminals in normal human subjects and IPD patients. In addition, ^{99m}Tc-TRODAT-1 is a promising ^{99m}Tc-labelled radiotracer for imaging DAT in the human brain. Since a cyclotron and well-trained radiochemists are required for clinical usage of ^{123}I-β-CIT and ^{123}I-FP-CIT SPECT, they are more difficult to use in clinical settings. ^{99m}Tc-TRODAT-1 is much easier to prepare and can be made in many nuclear medicine departments. Previous studies have shown that ^{99m}Tc-TRODAT-1 is very reliable in detecting dopamine neurons in the striatum; therefore, it is an important tool for understanding the role of DAT in various neurological diseases.

3. DAT scan in IPD

Similar to ^{123}I-β-CIT and ^{123}I-FP-CIT, ^{99m}Tc-TRODAT-1 activity in the basal ganglia can demonstrate a stable target/non-target ratio, and at a reduced level in IPD patients than in healthy volunteers. Serial ^{99m}Tc-TRODAT-1 SPECT images taken 2, 3, and 4 h after injection of 925 MBq ^{99m}Tc-TRODAT into healthy volunteers show a consistent increase of the uptake with time. Furthermore, the relative concentration of ^{99m}Tc-TRODAT-1 in the basal ganglia regions decreases significantly with age in healthy volunteers. The rate of decline is significantly faster in young individuals than in the elderly. The effect seems to occur during young adulthood, particularly in individuals younger than 40 years. The putamen/occipital and caudate/occipital ratios show a statistically significant difference between IPD patients and healthy volunteers.

4. Secondary parkinsonism

4.1 Toxin-induced PM
4.1.1 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

MPTP is a byproduct of a meperidine analogue, 1-methyl-4-proprion-oxypeperidine (MPPP), which is a synthetic heroin. Injection of the contaminated synthetic drug may cause the victims to develop acute severe parkinsonian features such as bradykinesia and severe rigidity in about 7 days. Since its discovery, MPTP has been used in animal models of

parkinsonism, which is responsive to dopamine and dopamine agonist treatment. Although dementia and autonomic dysfunction, typical dyskinesia, prominent wearing off phenomena, and psychiatric impairments in MPTP victims occur more rapidly than in subjects with IPD, the clinical features of these individuals are indistinguishable from those of IPD patients. The MPTP toxin may damage the dopamine neurons in the substantia nigra via 1-methyl-4-phenyl-pyridinium (MPP+), a metabolite of MPTP, that may inhibit the production of ATP and stimulate the formation of superoxide radicals. The neurotoxic effect of MPTP is permanent, even though the patients have an excellent response to levodopa treatment. 6F-Dopa positron emission tomography (PET) of the brain showed that a subclinical exposure to MPTP might result in a reduction of fluorodopa uptake in the striatum. In some experimental studies that used brain SPECT, ^{99m}Tc-TRODAT-1 binding was significantly lower in the MPTP-treated monkeys than in the control monkeys.

4.1.2 Manganese (Mn) intoxication

Chronic exposure to manganese may induce parkinsonism similar to IPD. However, the clinical features of manganism, including lower body parkinsonism, frequent gait disturbance (particularly cock gait), increased dystonia, and reduced action tremor, also differ from IPD. In addition, in Mn-induced PM, a reduced response to anti-parkinsonian drugs, gait-freezing during turns, and difficulty in walking backwards were also noted. Although relative symmetry was noted, clinical asymmetry was also reported. Unlike patients with multiple system atrophy, patients with manganism did not show postural hypotension, sexual dysfunction, and sphincter disturbance.

Brain magnetic resonance imaging (MRI) is a promising technique to demonstrate the presence of manganese in the brain. T1-weighted MR images showed an increased intensity in the globus pallidus area of welders, smelters, patients undergoing parenteral nutrition, and in patients with hepatic failure. However, the increase in signal intensity in T1-weighted MR images only indicates an exposure to manganese in recent months but does not indicate manganism.

Previous PET scans with 6-FD had shown a normal nigrostriatal dopaminergic uptake in the caudate or putamen in manganism patients. In addition, brain PET scans with raclopride showed a mild decrease (less than 20%) of caudate dopamine D2 receptors. However, the minimal decrease of D2 receptor density could not account for the prominent clinical features in manganese intoxication patients.

Both 6-FD PET and DAT are sensitive detectors for dopamine neurons. In a previous study, DAT density with ^{123}I-β-CIT SPECT was decreased in PM patients with manganese exposure. However, these findings seemed to be more consistent with IPD than with Mn-induced parkinsonism. The brain ^{99m}Tc-TRODAT-1 SPECT showed no significant changes in the putamen and the putamen/caudate ratio of manganism patients and normal controls. However, a statistically significant decrease was noted in the uptake of ^{99m}Tc-TRODAT-1 in the putamen area of IPD patients than in the manganism patients. Figure 1 shows the DAT findings in a manganism patient, an IPD patient, and a normal control. The data indicate that presynaptic dopaminergic terminals are not the main targets of chronic manganese intoxication. Pathologic changes in monkeys after manganese chloride injection included prominent gliosis in the globus pallidus and in the substantia nigra pars reticularis that differs from the target lesion-substantia nigra pars compacta in IPD.
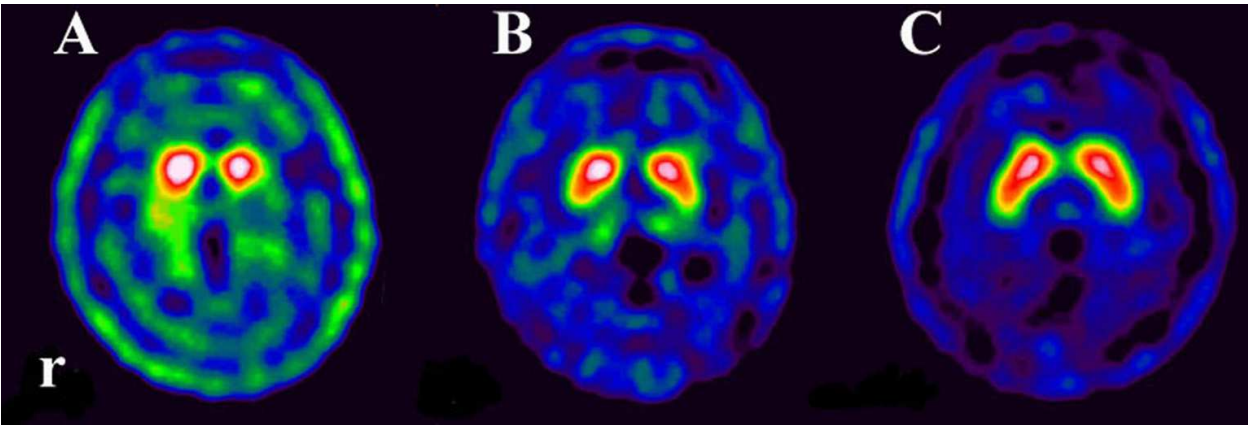
Fig. 1. The uptakes of ^{99m}Tc -TRODAT-1 brain SPECT were decreased in the corpus striatum particularly in the left side in a PD patient (A), and nearly normal in a patient with chronic manganism (B) and a normal control (C). r=right.

4.1.3 Carbon disulfide (CS_2) intoxication

CS_2 is a colorless liquid organic solvent frequently used in the production of viscose rayon fibers and cellophane films. Acute exposure to CS_2 may cause psychosis, delirium, seizures,
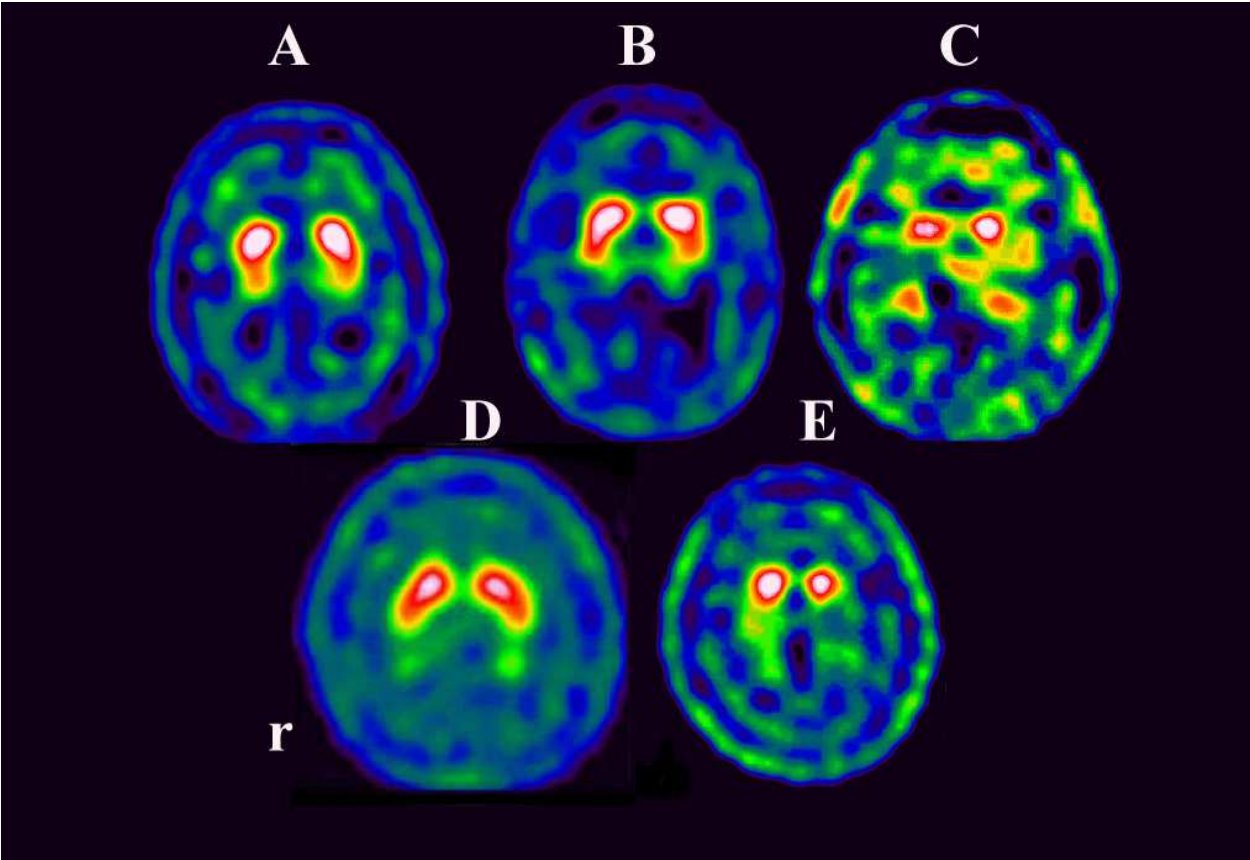

Fig. 2. Normal DAT bindings with ^{99m}Tc -TRODAT-1 brain SPECT were noted in 2 patients with CS_2 intoxication (A), and (B) but a decreased DAT binding in another patient who had IPD with CS_2 exposure (C), as compared with those of a normal control (D) and a PD patient (E). r=right.

and even death. Chronic exposure to CS_2 manifests as a diffuse encephalopathy including parkinsonism, intention tremor, emotional lability, and neurobehavioral disorders as well as polyneuropathy. Brain MRI may reveal diffuse hyperintense lesions in T2-weighted images in the subcortical white matter, basal ganglia, and brainstem. A brain CT perfusion study showed a decrease of regional cerebral flow and prolonged regional mean transit time in the subcortical white matter and the basal ganglia. The diffuse white matter lesions are better explained by vascular insufficiency than demyelination. In CS_2 intoxicated patients with parkinsonism, brain ^{99m}Tc-TRODAT-1 SPECT showed a normal uptake of the dopamine transporter, indicating a normal presynaptic dopaminergic pathway (Figure 2). Therefore, CS_2 intoxication-induced parkinsonism is probably due to post-synaptic lesions in the basal ganglia rather than the presynaptic dopaminergic pathway.

4.1.4 Carbon monoxide (CO) intoxication

Acute CO intoxication may induce hypoxic changes in the brain with variable degree of consciousness disturbance from confusion, delirium, and stupor to deep coma. Most patients recover after appropriate oxygen therapy; however, sequelae such as dystonia and cognitive impairment may persist. Approximately 0.2–40% of survivors developed delayed encephalopathy within 2 months. The common manifestations include cognitive changes, sphincter disturbance, akinetic mutism, and parkinsonian features. Brain MRI studies showed hyperintense lesions in the basal ganglia, particularly in the globus pallidus and subcortical white matter. A steady improvement was found after 1–2 years of supportive therapy; however, residual parkinsonism may develop in some patients. Moreover, a poor response to levodopa is noted. Brain ^{99m}Tc-TRODAT-1 may show a normal uptake in the basal ganglia, indicating that the presynaptic pathway of the nigrostriatral system is normal.

4.1.5 Others: Methanol and cyanide

Acute intoxication with methanol may cause metabolic acidosis and severe anionic gaps, leading to blindness and parkinsonism including masked face, rigidity, bradykinesia, gait disturbance, and dystonia. Brain MRI may show damage in the bilateral putaminal areas. Acute cyanide intoxication may also cause parkinsonism such as hypomimia, rigidity, and gait disturbance within a few days, and subsequent dystonia and dementia. The response to levodopa therapy is usually disappointing. Table 1 summarizes the clinical features and DAT findings in toxin-induced PM.

4.2 Other neurodegenerative parkinsonian syndromes
4.2.1 Progressive supranuclear palsy (PSP)

PSP, first described in the early 1900s, is a devastating neurodegenerative disease. In 1963, Steele, Richardson, and Olszewski reported a series of patients with pathologically confirmed heterogeneous system degeneration. The syndrome is characterized by parkinsonism, axial rigidity, frequent falls, vertical gaze palsy, pseudobulbar palsy, and dementia. In addition, atypical features include asymmetrical parkinsonism, dystonia, tremor, apraxia, and pure akinesia. The pathological changes include neuronal loss, neurofibrillary tangles, and gliosis in the basal ganglia, brainstem, and cerebral cortex. The response to levodopa treatment for parkinsonian symptoms is usually poor. The most

common subtypes of PSP syndrome include Richardson's syndrome (RS) and progressive supranuclear palsy-parkinsonism (PSP-P). The clinical features of RS are similar to the classic type of PSP, whereas PSP-P has features similar to IPD, such as asymmetric onset of symptoms, tremor, and initial response to levodopa.

	MPTP	Mn	CS$_2$	CO	Methanol
Clinical features					
Parkinsonism	+	+	+	+	+
Rigidity	+	+	+	+	+
Tremor	+	Less	-	-	-
Bradykinesia	+	+	+	+	+
Loss of postural reflex	+	+	+	+	+
Mental disorders	+	+	+	+	+
Cerebellar sign	-	Less	+	-	-
Polyneuropathy	-	-	+	-	-
Autonomic dysfunction	+	+	+	-	-
Neuroimaging					
Brain CT/MRI	N/N	N/+ (T1 high)	+/+ (Vascular changes)	+/+ (GP)	+/+ (Putamen lesion)
DAT uptake in striatum (^{99m}Tc-TRODAT-1 SPECT)	Decrease (in monkey)	N	N	N	NA
Prognosis	Permanent	Deterioration	Poor	Partial recovery	Blindness
Response to Levodopa	Good	No	No	No	Poor
Source of exposure	Synthetic heroin	Smelter, miner, welder	Viscose rayon worker	Accidental, suicidal attempts	Accidental

+: presence; -: absence; GP: globus pallidus; N: normal; NA: not available
MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; Mn: manganese; CS$_2$: carbon disulfide; CO: carbon monoxide.

Table 1. Toxins induced secondary parkinsonism

Dopamine transporter (DAT) scans with ^{123}I-β-CIT showed a reduction of DAT activities in the caudate and putamen areas, particularly the caudate areas in PSP patients. However, the dopamine D2 receptor images with IBZM were variable. The inconsistent findings are probably because of the grouping of both RS and PSP-P types. In our previous studies with

99mTc-TRODAT-1 scans, the mean striatal uptake was reduced in the RS group than in the PSP-P group, even though uptake did not reach statistical significance. The putamen/caudate ratios were significantly different between IPD and PSP patients. However, there was no difference between RS and PSP-P patients. In the IBZM scan, the uptake was significantly reduced in the RS group, but mildly increased in the PSP-P group. The data indicate that DAT imaging is helpful to distinguish PSP-P from IPD patients in the early stages. DAT activities showed a greater decrease in the RS group than in the PSP-P group. In addition, activities of the D2 receptor were reduced in the RS group but not in the PSP-P group.

4.2.2 Multiple system atrophy (MSA)

Multiple system atrophy (MSA) was originally described as 3 distinct disorders: olivopontocerebellar atrophy (OPCA), Shy–Drager syndrome (SDS), and striatonigral degeneration (SND). MSA is a sporadic progressive neurodegenerative disease characterized by variable degrees of parkinsonism, cerebellar ataxia, and autonomic dysfunction. According to the motor dysfunction, MSA can be divided into 2 subtypes: parkinsonian type (MSA-P) and cerebellar type (MSA-C). The pathologic changes reveal a variable involvement of neuronal loss in the corpus striatum, globus pallidus, substantia nigra, locus ceruleus, Edinger–Westphal nucleus, olivary nuclei, cerebellar peduncles, cerebellar Purkinje cells, intermediolateral column, and Onuf's nucleus of the spinal cord. The diagnosis of MSA is still based on clinical criteria. The clinical distinction between MSA-P and IPD is sometimes difficult, particularly in the early stages, because both have a good response to levodopa.

In IPD patients, a severe reduction of DAT uptake in the putamen and relative sparing of the caudate nucleus is noted. However, a variable uptake of 6-^{18}F-fluorodopa was noted in MSA patients. 99mTc-TRODAT-1-brain SPECT revealed a more symmetrical reduction of the striatal binding in MSA-P and MSA-C patients; this was in contrast with the greater asymmetric reduction seen in IPD patients. In addition, the reduction of P/O and S/O ratios is greater for the MSA-P patients than for the MSA-C patients. P/C ratios showed that MSA-P and IPD patients have a similar pattern of nigral involvement but that MSA-C patients had a different pattern.

4.2.3 Spinocerebellar degeneration (SCA)

Hereditary ataxias are a clinically and genetically heterogeneous group of disorders transmitted most frequently as autosomal dominant or autosomal recessive traits. Three common phenotypes including SCA1, SCA2 and SCA3 (Machado–Joseph disease, MJD) are characterized by variable degrees of cerebellar signs, pyramidal dysfunction, anterior horn cell involvement, and/or peripheral neuropathy but some patients may develop parkinsonian symptoms, which may also respond to levodopa treatment.

4.2.3.1 SCA1

The early pictures include cerebellar syndrome and upper motor neuron signs. Later, ophthalmoplegia, slow saccades, and a sensory predominant polyneuropathy, amyotrophy, chorea, and dystonia may develop. Dysarthria, dysphagia, and cognitive impairment are also noted. The gene mutation is an unstable CAG expansion in the *ataxin 1* gene on chromosome 6p. Brain 99mTc-TRODAT-1 SPECT imaging revealed a decrease of dopamine transport in the striatum.

4.2.3.2 SCA2

SCA2 has a wider phenotypical spectrum than SCA1. The presence of slow saccades and peripheral neuropathy early in the disease may lead to the diagnosis of SCA2. In addition, dystonia, levodopa-responsive parkinsonism, and cognitive decline are also noted. The mutation is a CAG expansion in the *ataxin 2* gene on chromosome 12 with alleles ranging from 32–64 (normal, 15–31). 99mTc-TRODAT-1 SPECT of the brain showed a significantly asymmetric reduction of the striatal dopamine transporter in these patients; this was similar to the finding in IPD patients. The presynaptic impairment of nigrostriatal function is probably the reason for levodopa responsiveness.

4.2.3.3 SCA3

This is the most prevalent type of spinocerebellar ataxia. The clinical manifestations include cerebellar and brainstem signs such as facial and tongue fasciculations or myokymia, with facial atrophy, and dysphonia. Non-cerebellar eye signs such as slow saccades, impairment in conjugate eyeball movement, ophthalmoparesis, ptosis, eyelid retraction, and blepharospasm have also been reported. Dystonia is commonly seen. In addition, the parkinsonian features may respond to dopamine therapy. The mutation is an unstable CAG expansion in the *ataxia 3* gene on chromosome 14 with 53–86 CAG repeats (normal limit < 47). 99mTc-TRODAT-1 scan of the brain revealed a significant decrease in the uptake of tracers in MJD patients than in healthy controls. The decreased uptakes of 99mTc-TRODAT-1 indicated a defect in the nigrostriatal dopaminergic pathway in symptomatic MJD patients with and without extrapyramidal signs. However, the severity of the DAT abnormality did not correlate well with the length of the CAG repeat, age at disease onset, or disease duration.

4.2.4 Corticobasal syndrome (CBS)

Corticobasal syndrome was first described in 1967 in 3 patients who had asymmetric motor symptoms with an involvement of frontoparietal atrophy and neuronal loss at autopsy. CBS is an adult onset and slowly progressive degeneration with asymmetric akinetic-rigid syndrome. A limited response to levodopa treatment is noted in such patients. Some other extrapyramidal symptoms include tremor, dystonia, cortical dysfunction, cortical sensory impairment, apraxia, and alien hand phenomenon. Brain MRI may show focal cortical atrophy, particularly in the parietal lobe. Brain 18F-FDG PET reveals a frequently asymmetric hypometabolism in both the cerebral hemispheres. Brain 99mTc-TRODAT SPECT reveals an asymmetric involvement in the corpus striatum with equal involvement in both caudate and putamen regions.

The clinical and DAT findings in the above-described neurodegenerative diseases are shown in Table 2.

4.3 Gene-related parkinsonism/dystonia degenerative diseases
4.3.1 Dopa-responsive dystonia (DRD)

Dopa-responsive dystonia, also known as Segawa's disease, is characterized by foot dystonia since childhood, diurnal fluctuation, and a dramatic and sustained response to low-dosage levodopa. Some patients with DRD may also show adult-onset parkinsonism similar to IPD. Pathologic degeneration of dopaminergic nigral cells is found in IPD, whereas synthesis defects in dopamine neurons without cell loss are noted in DRD.

	PSP		MSA		SCA			CBS
	RS	PSP-P	MSA-P	MSA-C	SCA1	SCA2	SCA3	
Clinical features								
Parkinsonism	+(sym)	+(asym)	+	+	+	+	+	+ (asym)
Rigidity	+(axial)	+(axial)	+	+	+	+	+	+ (asym)
Tremor	-	+	+	+	+ (action)	+ (action)	+ (action)	+
Bradykinesia	+	+	+	+	+	+	+	-
Loss of postural reflex	+	+	+	+	+	+	+	-
Akinetic- rigid syndrome	+	-	+	-	-	-	-	+
Dystonia	+(facial)	+(facial)	-	-	+	+	+	+
Retrocollis	+	+	- (anticollis)	-	-	-	-	-
Cognitive dysfunction	+	+	+	-	+	-	-	+
Alien hand	-	-	-	-	-	-	-	+
Cortical sensory impairment	-	-	-	-	-	-	-	+
Cerebellar sign	-	-	+	+	+	+	+	-
Ataxia	-	-	-	+	+	+	+	-
Slow saccade	-	-	-	-	+	+	+	-
Peripheral neuropathy	-	-	-	-	+	+	-	-
Autonomic dysfunction	+	+	+	+	-	?	?	?
EOM limitation	+ (VGP)	+ (VGP)	-	-	+	-	+	-
Ptosis	-	-	-	-	-	-	+	-
Fasciculation	-	-	-	-	-	-	+	-
Face	-	-	-	-	-	-	+	-
Tongue	-	-	-	-	-	-	+	-
Dysarthria	+	+	+	+	+	+	+	-
Dysphagia	+	+	+	+	+	+	+	-
Apraxia	-	-	-	-	-	-	-	+
Response to Levodopa	Poor	Initial good	Initial good	Partial	Partial	Initial good	Partial	+ (limited)
Neuroimaging								
CT/MRI	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+
DAT uptake	D	D	D (sym)	D (sym)	D	D (asym)	D	D (asym)
IBZM uptake	D	Increase (mild)	Possible D	Possible D	NA	NA	NA	D
6 FD-PET uptake	NA	NA	D	D	NA	NA	NA	D (asym)

+: presence; -: absence; D: decrease; I: increase; sym: symmetrical; asym: asymmetrical; VGP: vertical gaze palsy; NA: not available

Table 2. Clinical features and DAT data in neurodegenerative diseases

Molecular genetic studies revealed a mutation in GTP cyclohydrolase 1 (*GCH1*) in autosomal-dominant inherited DRD and mutations in tyrosine hydroxylase (*TH*) in autosomal-recessive inherited DRD. In DRD patients, ^{18}F-Dopa PET reveals normal uptakes in the corpus striatum; these findings may distinguish DRD from IPD, which reveals a decreased uptake even in the early stage of IPD patients. Dopamine transporter images with ^{99m}Tc-TRODAT-1 SPECT also show a normal uptake in DRD, indicating that presynaptic nigrostriatal dopaminergic terminals are normal (Figure 3).

Fig. 3. The [99m]Tc -TRODAT-1 brain SPECT shows a normal uptake in the putamen and caudate in a patient with DRD (B) compared with those in a normal control (A) and a PD patient (C). A reduction of the uptake in the corpus striatum, particularly in the right side was observed in the PD patient. r=right.

4.3.2 Wilson's disease (WD)

Wilson's disease, hepatolenticular degeneration, is an autosomal recessive disorder characterized by a decreased serum concentration of ceruloplasmin, low serum copper concentration, and excessive deposition of copper in the liver, brain, and other organs.

The most common neurological manifestations include akinetic-rigid syndrome, dystonia, and cerebellar ataxia with action tremor. Pathologically, the most severely affected lesions include the basal ganglia involving the putamen, caudate, and globus pallidus. A brain CT scan may show low-density lesions with cystic degeneration in the basal ganglia, particularly the putamen and globus pallidus, as well as cortical atrophy and ventricular enlargement. Brain MRI reveals increased signal intensities in T2-weighted images of the lenticular nuclei, thalamus, and brainstem including the pons, midbrain, and even the substantia nigra. Occasionally, double panda signs were found in the brainstem. A poor therapeutic response to levodopa is noted in WD patients. However, brain 6F-DOPA PET studies have shown an involvement of the nigrostriatal presynaptic dopaminergic pathway. In addition, SPECT with ^{123}I-iodobenzamide (^{123}I-IBZM) and PET images with ^{18}F-methylspiperone have showed a reduction of postsynaptic striatal D2 receptor, reflecting striatal neuronal damage. Some DAT studies with ^{123}I-β-CIT SPECT disclosed a severe or differential loss of the DAT in the striatum of WD patients, indicating a presynaptic defect in the terminals of the nigrostriatal dopaminergic neurons. However, in some WD patients with akinetic-rigid syndrome, a normal presynaptic dopaminergic pathway may occur; brain MRI also reveals the involvement of substantia nigra in these patients. (Figure 4).
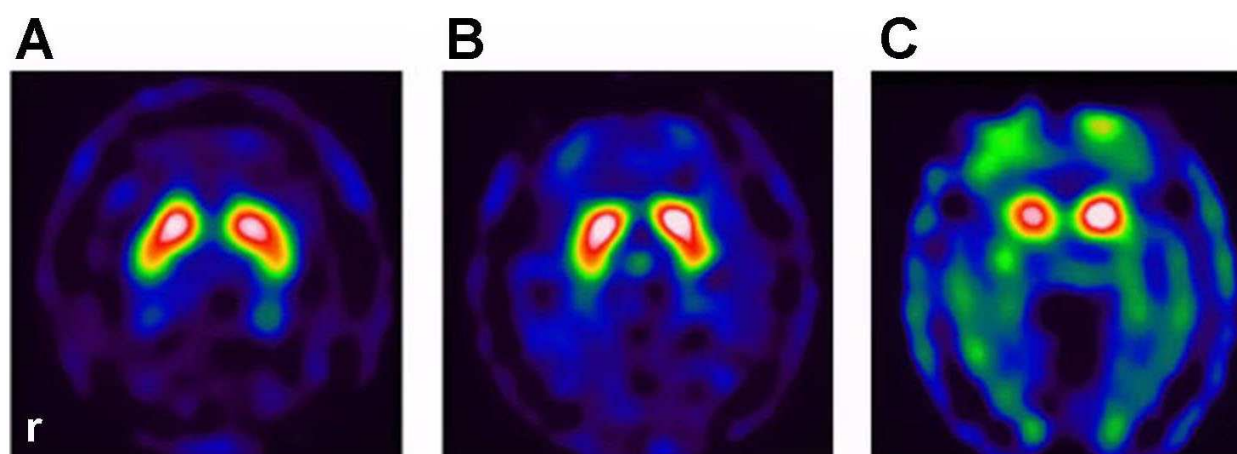
Fig. 4. Demonstration of ^{99m}Tc-TRODAT-1 uptake in an age-matched normal control (A), a WD patient (B) and a PD patient (C). Normal uptake of ^{99m}Tc-TRODAT-1 in the putamen and caudate nucleus was noted in a normal control and a WD patient (A and B). In PD patient, there was an asymmetrically decreased ^{99m}Tc-TRODAT-1 uptake, predominantly in the putamen (C). r=right.

4.3.3 Huntington's disease (HD, Westphal type)

Huntington's disease, the most common cause of hereditary chorea, is an autosomal dominant disorder caused by an expansion of an unstable trinucleotide repeat in chromosome 4. The most striking feature is the appearance of chorea movements that seem purposeless and abrupt. However, some patients may present with the so-called akinetic-rigid variant form (Westphal variant). This form of the disease is rapidly progressive with a fatal outcome in less than 10 years after the onset of symptoms. Brain CT/MRI show enlarged ventricles with atrophy of the caudate nucleus. MRI of patients with the a kinetic-rigid form of the disease may reveal T2 hyperintense lesions in the striatum. FDG-PET may show hypometabolism in the caudate and putamen regions.

The clinical features and neuroimages of DRD, WD, and HD with Westphal variant are summarized in Table 3.

4.4 Dementia syndromes with parkinsonism
4.4.1 Vascular parkinsonism (VP) or multiple infarct parkinsonism

Vascular parkinsonism is characterized by clinical symptoms of gait disturbance with freezing, lower body parkinsonism, and loss of postural reflexes. Tremor is rarely seen. The onset is usually insidious and the course is progressive. Brain MRI usually reveals hyperintense T2-weighted signals in the basal ganglia and/or white matter; these findings are compatible with those of multiple infarctions. Hypertension is a common risk factor for the disorder. A poor or insufficient response to anti-parkinsonian drugs is also noted in these patients. Early diagnosis of VP is important because the prognosis and response to treatment in these patients are different from those of patients with IPD. However, VP may have a wide spectrum of clinical features, which make the differential diagnosis of these diseases difficult. A study using DAT with ^{99m}Tc-TRODAT-1 showed that specific binding in the putamen and caudate areas was slightly lower in VP patients than in healthy individuals; however, a significant decrease in the uptake of ^{99m}Tc-TRODAT-1 in the

striatum was noted in IPD patients. A significant striatal asymmetry was observed in IPD patients but not in VP patients.

	DRD	WD	HD (Westphal)
Clinical features			
Diurnal fluctuation	+	-	-
Chorea	-	-	+
Dystonia	+	+	+
Parkinsonism	+	+	+
Cerebellar sign	-	+	-
Cognitive impairment	-	+	+
Liver dysfunction	-	+	-
Autonomic dysfunction	-	+	-
Response to levodopa	Excellent	Partial	No
Neuroimaging			
CT/MRI	N/N	Abn/Abn	Abn/Abn (caudate atrophy)
DAT-SPECT	N	Abn	NA
FDG-PET	N	Abn	Abn
6 FD-PET	N	Abn	NA

+: presence; -: absence; N: normal; Abn: abnormal; NA: not available

Table 3. Clinical features and DAT findings in gene- related PM/dystonia degenerative diseases

4.4.2 Dementia with Lewy bodies (DLB)

DLB is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD). The diagnostic criteria of DLB were established by the consensus conference for DLB in 2005. In the early stage of DLB, deficits in attention, executive function, and visuospatial ability are very prominent. The core clinical features include fluctuation of cognition, visual hallucination, and spontaneous parkinsonism. Recent suggestive features include REM sleep behavioral disorder, severe neuroleptic sensitivity, and low dopamine transporter uptake in the basal ganglia on SPECT or PET imaging. Supportive features of DLB diagnosis include repeated falls, syncope, transient loss of consciousness, autonomic dysfunction, depression, systematized delusions, or hallucinations. In brain MRI, atrophy of the cortical or hippocampus is lower in DLB patients than in AD patients. In ^{18}F-FDG PET or SPECT, maximal hypometabolism was noted in the parieto-occipital area in DLB patients; however, maximal hypoperfusion was noted in the tempo-parietal cortex in AD patients.

Serial DAT with I-[123] β-CIT brain SPECT also demonstrated progressive striatal dopaminergic loss in DLB and Parkinson's disease with dementia, but not in AD. These findings have a high specificity (94%) in distinguishing between DLB and AD.

A brain DAT with TRODAT-1 SPECT also demonstrated a decreased uptake in the striatum, including the putamen and caudate regions, but the DLB patients had relatively symmetric lesions and IPD patients had asymmetric lesions.

4.4.3 Frontotemporal dementia with parkinsonism-17 (FTDP-17)

Frontotemporal dementia (FTD) can be divided into 3 major subtypes, including frontotemporal lobe dementia (FTLD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA). The characteristic behavior changes include disinhibition, social withdrawal, diminished insight, loss of empathy, perseverance, and stereotypic behaviors. Semantic dementia may present with progressive loss of semantic knowledge, and although speech remain fluent, it becomes empty. Semantic dementia usually manifests as a fluent

	VaD	DLB	FTDP-17
Clinical features			
Parkinsonism	+	+	+
Rigidity	+	+	+
Tremor	-	-	-
Bradykinesia	+	+	+
Lose of postural reflex	+	+	+
Language problem	+	-	+
Focal sign	+	-	+
Dysarthria	+	-	-
Dysphagia	+	-	-
Dementia	+	+	+
Hallucination	+	+	-
Cognitive fluctuation	-	+	-
Personality changes	+	+	+
Syncope	-	+	-
Autonomic dysfunction	-	+	-
Response to levodopa	Poor	Poor	Poor
Neuroimages			
CT/MRI	Abn/Abn	Abn/Abn	Abn/Abn
DAT-TRODAT	Normal	Abn	NA
FDG-PET	Abn	Abn	Abn
6FD-PET	NA	Abn	NA

+: Presence; -: absence; Abn: abnormal; NA: not available

Table 4. Clinical features and DAT findings in dementia syndromes

dysphasia with impairment in semantic verbal memory and an associative agnosia in individuals with more left temporal lobe involvement. Prosopagnosia may occur with right temporal damage. Progressive non-fluent aphasia is characterized by aphasia with stuttering and agrammatism. The executive function and working memory are usually impaired. The typical neuroimaging findings are asymmetrical atrophy of the anterior temporal lobe in SD and atrophy of the left inferior frontal lobe and anterior insular cortex in PNFA. In addition, there is overlap of clinical manifestations between AD and FTD. These 3 subtypes of FTD often overlap motor syndromes such as amyotrophic lateral sclerosis (ALS) and parkinsonism.

FTDP-17 is a distinct disease characterized by personality changes, executive dysfunction, memory deterioration, and parkinsonism. Motor disturbances include bradykinesia, axial and limb rigidity, and postural instability. Early manifestations include behavioral changes such as disinhibition, impaired social function, judgment and planning, and global dementia. Parkinsonism in FTDP-17 is unresponsive to levodopa. Table 4 summarizes the clinical manifestations in vascular parkinsonism, DLB, and FTDP-17.

5. Conclusion

The clinical features of IPD and PM are very similar, but some manifestations differ. The treatment and prognosis also differ. The response to treatment with levodopa is variable; therefore, definite diagnosis is very important. Early and accurate differentiation between IPD and PM has been markedly improved by recent developments in neuroimaging, particularly the ^{99m}Tc-TRODAT-1 SPECT, which is not only easy and economical to prepare and use in a wide variety of applications but also reliable in understanding the role of DAT in various neurological diseases. Most importantly, early and correct diagnosis leads to earlier and, therefore, more effective treatment with levodopa, when appropriate.

Abbreviations:

CBS: corticobasal syndrome
β-CIT: (1r) 2β-carbomethoxy-3β-(4-iodophenyl) tropane
CO: carbon monoxide
CS_2: carbon disulfide
DAT: dopamine transporter
DRD: dopa-responsive dystonia
DLB: dementia with Lewy bodies
6-FD: 6-fluorodopa
FDG: fluorodeoxyglucose
FTD: frontotemporal dementia
FTDP-17: frontotemporal dementia with parkinsonism linked to chromosome 17
HD: Hungtington's disease
^{123}I-IBZM scan: I-123–iodobenzamide D_2 receptor scan
IPD: idiopathic Parkinson's disease
MJD: Machado–Joseph disease
Mn: manganese
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MSA: multiple system atrophy
MSA-C: multiple system atrophy-cerebellar subtype
MSA-P: multiple system atrophy-parkinsonism subtype
PET: positron emission tomography
PM: Parkinsonism
PSP: progressive supranuclear palsy
PSP-P: progressive supranuclear palsy-parkinsonism
RS: Richardson syndrome
SCA: spinocerebellar atrophy
SPECT: single photon emission computed tomography
99mTc-TRODAT-1: Tc-99m labeled radiotracer for imaging DAT
VP: vascular parkinsonism
WD: Wilson's disease

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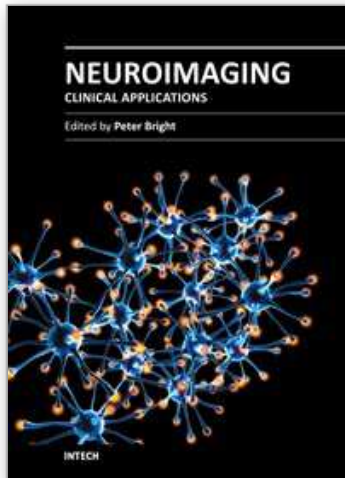## Frontotemporal dementia

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