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## Role of Neuroimaging on Differentiation of Parkinson's Disease and Its Related Diseases

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### ABSTRACT

An accurate diagnosis of Parkinson's disease (PD) is a prerequisite for therapeutic management. In spite of recent advances in the diagnosis of parkinsonian disorders, PD is misdiagnosed in between 6 and 25% of patients, even in specialized movement disorder centers. Although the gold standard for the diagnosis of PD is a neuropathological assessment, neuroimaging has been playing an important role in the differential diagnosis of PD and is used for clinical diagnostic criteria. In clinical practice, differential diagnoses of PD include atypical parkinsonian syndromes such as dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, caused by a striatal dopamine deficiency following nigrostriatal degeneration. PD may also be mimicked by syndromes not associated with a striatal dopamine deficiency such as essential tremor, drug-induced parkinsonism, and vascular parkinsonism. Moreover, difficulties are associated with the clinical differentiation of patients with parkinsonism from those with Alzheimer's disease. In this review, we summarize the typical imaging findings of PD and its related diseases described above using morphological imaging modalities (conventional MR imaging and neuromelanin MR imaging) and functional imaging modalities ( $^{99m}\text{Tc}$ -ethyl cysteinate dimer perfusion single photon emission computed tomography,  $^{123}\text{I}$ -metaiodobenzylguanidine myocardial scintigraphy,

and  $^{123}\text{I}$ -FP-CIT dopamine transporter single photon emission computed tomography) that are clinically available in most hospitals. We also attempt to provide a diagnostic approach for the differential diagnosis of PD and its related diseases in clinical practice.

**Key words** atypical parkinsonian syndrome;  $^{123}\text{I}$ -FP-CIT dopamine transporter imaging;  $^{123}\text{I}$ -metaiodobenzylguanidine myocardial scintigraphy; neuromelanin-sensitive MR imaging; Parkinson's disease

An accurate diagnosis of Parkinson's disease (PD) is a pre-requisite for patient therapeutic management. However, the overall quality of the clinical diagnosis of PD is inadequate, even in tertiary centers with movement disorder experts. Only 8 out of 10 patients with parkinsonism have a valid diagnosis.<sup>1,2</sup> In early disease stages, the differentiation between PD and atypical parkinsonian syndromes such as dementia with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), caused by nigrostriatal degeneration may be challenging in clinical practice.<sup>3</sup> PD may also be mimicked by syndromes not associated with a striatal dopamine deficiency such as essential tremor (ET), drug-induced parkinsonism, and vascular parkinsonism (VP).<sup>4,5</sup> Moreover, difficulties are sometimes associated with the clinical differentiation of patients with parkinsonism from those with Alzheimer's disease (AD) because of overlapping clinical and pathological features.<sup>2,6,7</sup>

In spite of recent advances in the imaging and genetics of parkinsonian disorders, the diagnosis of PD remains a primarily clinical exercise. In an attempt to target this pitfall, numerous ancillary investigations have been developed in the last decade to support a PD diagnostic work-up.<sup>1</sup> Postuma et al. have recently proposed criteria intended to be used as the official International Parkinson and Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD (MDS-PD Criteria).<sup>8</sup> However, neuroimaging findings play only a limited role in this criteria. Strategies to develop biomarkers for the

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Abbreviations: AD, Alzheimer's disease; CBD, corticobasal degeneration; DaT, dopamine transporter; DaTSCAN, dopamine transporter SPECT; DLB, dementia with Lewy bodies; DTI, diffusion-tensor imaging; ET, essential tremor; FLAIR, fluid-attenuated inversion recovery; FDG,  $^{18}\text{F}$ -fluorodeoxyglucose; FP-CIT,  $^{123}\text{I}$ -2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)-N-(3-fluoropropyl) nortropane; HMPAO,  $^{99m}\text{Tc}$ -hexamethyl propylene amine oxime; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; MSA, multiple system atrophy; NmMRI, neuromelanin-sensitive MR imaging; PD, Parkinson's disease; PET, positron emission computed tomography; PSP, progressive supranuclear palsy; SPECT, single photon emission computed tomography; VBM, voxel-based morphometry; VP, vascular parkinsonism

diagnosis of PD, particularly to enable a diagnosis early in the disease course, even before the onset of motor symptoms, are still under investigation.<sup>9</sup>

The aim of this review is to describe typical neuroimaging findings of PD and its related diseases. We also stress the significance of neuroimaging in the differential diagnosis of PD and its related diseases and attempt to provide a diagnostic approach for a differential diagnosis in clinical practice.

## PD AND ITS RELATED DISEASES

The majority of neurodegenerative diseases have been characterized by the deposition of insoluble protein in the brain.  $\alpha$ -Synuclein is a major component of Lewy bodies and tau is a principal component of neurofibrillary and glial tangles. Synucleinopathies are neurodegenerative diseases characterized by the abnormal accumulation of aggregates of  $\alpha$ -synuclein in neurons, nerve fibers or glial cells. Tauopathies are a class of neurodegenerative diseases associated with the pathological aggregation of tau protein in neurofibrillary or gliofibrillary tangle. Main tauopathies consist of PSP, CBD, AD, and frontotemporal degeneration, while the main synucleinopathies with parkinsonism are PD, DLB, and MSA.

Parkinsonian syndromes are a group of movement disorders characterized by classical motor symptoms such as tremors, bradykinesia, and rigidity. They are most frequently due to primary neurodegenerative disease, resulting in the loss of dopaminergic nerve terminals along the nigrostriatal pathway, similar to idiopathic PD, MSA, PSP, CBD, and DLB. Other causes of parkinsonism that do not involve nigrostriatal degeneration include drug-induced, vascular, and psychogenic diseases as well as ET.<sup>10</sup>

Non-motor features such as cognitive impairment are common in early PD. Dementia is particularly prevalent, occurring in 83% of patients with PD who have had a disease duration of 20 years.<sup>9</sup> Therefore, PD and its related neurodegenerative diseases may also be included in the differential diagnosis of dementia. The clinical distinction between DLB and AD is sometimes difficult and DLB is most often misdiagnosed as AD.<sup>11</sup>

From the viewpoint of clinical differentiation, this review includes PD, atypical parkinsonian disorders (DLB, MSA, PSP, and CBD), ET, VP, and AD.

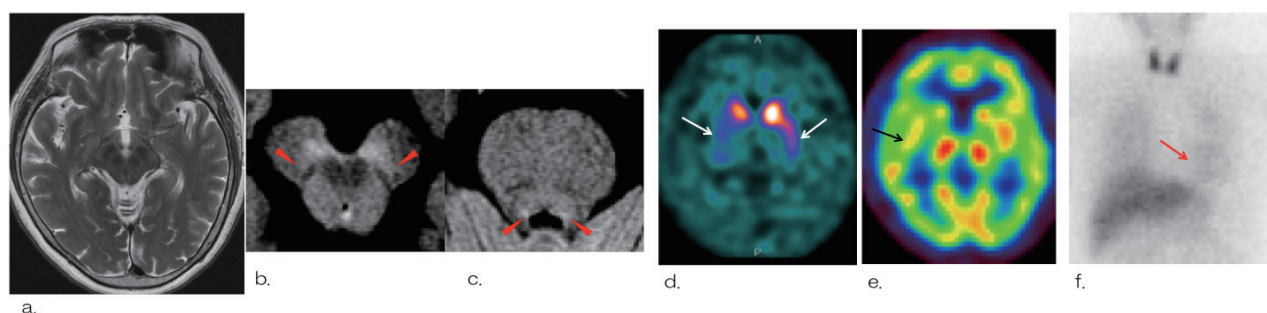
## IMAGING TECHNIQUES

Advances have been made in neuroimaging techniques for atypical parkinsonism in recent years. Neuroimaging findings may strongly support clinical diagnoses, which is crucial for prospective care planning. Nevertheless, in-

creasing information on the mixed pathologies and overlapping clinical presentations of these disorders make precise differentiation difficult.<sup>12</sup> Standardized imaging protocols for anatomic and functional imaging of the brain are essential for the reliable and accurate diagnosis of PD and its related diseases as well as for longitudinal studies evaluating disease progression in the clinical and research realms.<sup>13</sup> Berg et al. stressed an urgent need for reassessing the definition including neuroimaging for the diagnosis of PD.<sup>14</sup>

Conventional MR imaging may show abnormalities that are suggestive of neurodegenerative atypical parkinsonism.<sup>15</sup> Robust data emerging from routine MR imaging and many advanced MR imaging techniques such as diffusion-weighted imaging, diffusion-tensor imaging (DTI), magnetic resonance spectroscopy, voxel-based morphometry (VBM), susceptibility-weighted imaging, and neuromelanin-sensitive MR imaging (NmMRI) may contribute to a differential diagnosis. Kitao et al. reported that NmMRI visualizes neuromelanin-containing neurons in the substantia nigra pars compacta and is useful for the evaluation of parkinsonism.<sup>16</sup> The diagnosis of PD and its neurodegenerative diseases may be improved by applying new MR imaging techniques and modifying the conventional sequences described above. Moreover, the use of 7T MR imaging scanners may strengthen the diagnostic value, but are not yet widely available.<sup>12, 17, 18</sup>

In contrast, molecular imaging techniques may provide useful neurochemical information for learning about the pathophysiology of the disorder, diagnosing conditions at the early stages, monitoring disease progression, and planning and assessing responses to medical and surgical interventions, including the identification of potential targets for neuromodulation. In recent decades, positron emission computed tomography (PET) molecular imaging has provided a better understanding of the pathophysiological mechanisms underlying atypical parkinsonism.<sup>19</sup> However, PET typically depends on an adjacent cyclotron. Thus, the availability of single photon emission computed tomography (SPECT) is generally greater than that of PET.<sup>20</sup> Regional brain perfusion has been extensively investigated with the SPECT tracer <sup>99m</sup>Tc-hexamethyl propylene amine oxime (HMPAO).<sup>20</sup> <sup>123</sup>I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy and <sup>123</sup>I-2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)-N-(3-fluoropropyl) nortropine (FP-CIT) dopamine transporter SPECT (DaTSCAN) may become more widely available to assist in the diagnosis of patients with parkinsonian syndromes in many hospitals, because positive cardiac sympathetic denervation on MIBG myocardial scintigraphy is taken up for supportive criteria and normal presynaptic dopaminergic system



**Fig. 1.** Parkinson's disease in a 65-year-old female. (a) A T2-weighted MR image demonstrates no definite abnormalities including the midbrain. (b, c) NmMRI shows decreased hyperintensity in the lateral part of the substantia nigra (arrowheads) and locus coeruleus (arrowheads). (d) Markedly decreased striatal DaT uptake (arrows) is observed, particularly on the right side. (e) Perfusion SPECT shows mild hypoperfusion of the right basal ganglia (arrow). (f) Myocardial MIBG uptake (arrow) is markedly decreased. DaT, dopamine transporter; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; NmMRI, neuromelanin-sensitive MR imaging; SPECT, single photon emission computed tomography.

on DaTSCAN is taken up for absolute exclusion criteria in MDS-PD criteria.<sup>8</sup>

In this review, we mainly describe the imaging findings on conventional MR imaging, NmMRI and perfusion SPECT, DaTSCAN, and MIBG myocardial scintigraphy of PD and its related diseases.

## IMAGING FINDINGS

### PD (Fig. 1)

Conventional MR imaging is generally not helpful in the diagnosis of early PD because it frequently yields normal findings.<sup>21</sup> Since conventional MR imaging is useful for the appreciation of features suggestive of atypical parkinsonian disorders, the primary use of MR imaging is to exclude specific structural abnormalities that may potentially mimic PD.<sup>22</sup>

Magnetization transfer MR imaging and DTI demonstrated a lower magnetization transfer ratio and fractional anisotropy in the substantia nigra of PD patients than in healthy controls.<sup>22</sup> VBM in patients with PD indicates a paucity of gray matter atrophy in the early clinical phase.<sup>22</sup> Although these findings are useful as a group study, their application to individual patients may be difficult. NmMRI shows reductions in the hyperintense signal in the substantia nigra, particularly its lateral portion, and in the locus coeruleus. These findings are useful for the diagnosis and evaluation of the disease progression of PD.<sup>16, 23, 24</sup> The visualization of nigrosome 1, a substructure of the substantia nigra pars compacta undergoing the greatest and earliest dopaminergic cell loss in PD, on MR imaging is expected to result in the development of a neuroimaging diagnostic test for PD.<sup>5, 25, 26</sup>

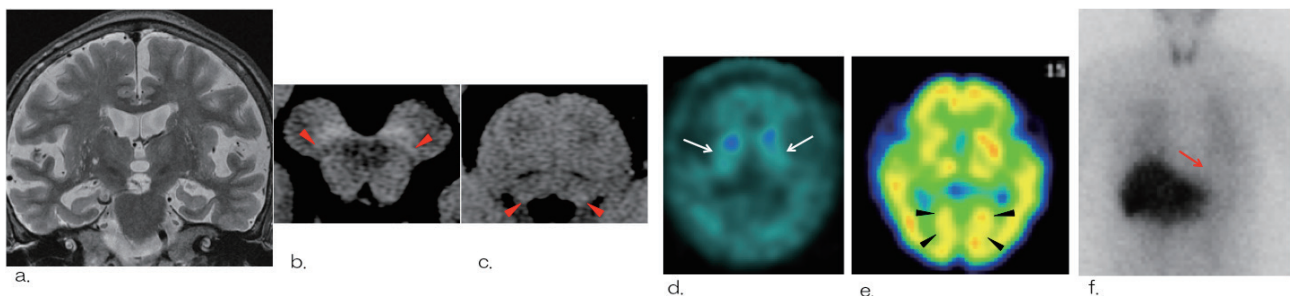
DaTSCAN demonstrates nigrostriatal dysfunction typical of PD as a decrease in the uptake of the radiotracer in the neostriatum with a predominantly early

deficiency in the putamen and often an asymmetric distribution.<sup>27</sup> Dopamine transporter (DaT) uptake is more prominently reduced in the putamen than in the caudate. DaTSCAN may accurately differentiate between early PD and secondary parkinsonian conditions, namely vascular or drug-induced parkinsonism and ET.<sup>27</sup> However, DaTSCAN approaches alone are not sufficient to diagnose PD because they do not reliably distinguish PD from other parkinsonian syndromes associated with nigrostriatal degeneration, such as atypical parkinsonism.<sup>9</sup>

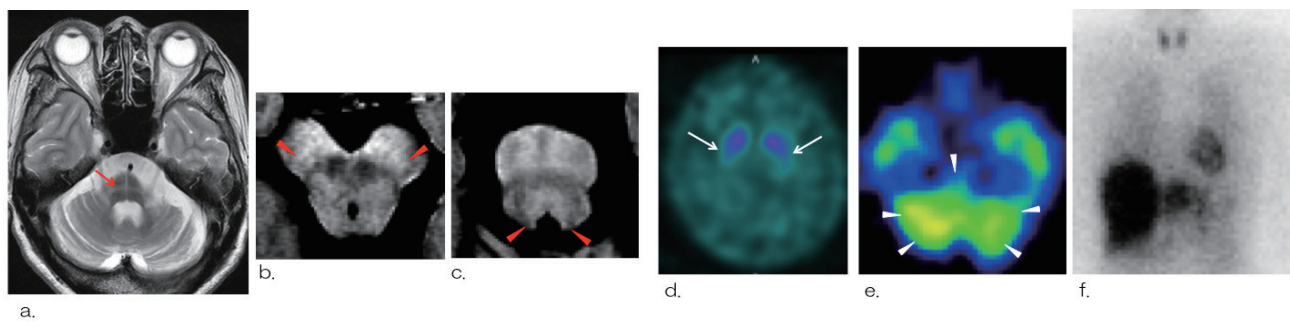
PD shows a characteristic impairment in adrenergic function that may be demonstrated by simple planar scintigraphy of the chest to reveal the lack of myocardial MIBG uptake.<sup>22</sup> This abnormality is not observed in other types of neurodegenerative parkinsonisms including PSP, MSA, and CBD.<sup>22</sup> Therefore, MIBG myocardial scintigraphy is useful for differentiating PD from other parkinsonisms, particularly neurodegenerative parkinsonism. Perfusion SPECT using statistical parametric mapping in PD patients compared with healthy subjects showed significant hypoperfusion in the basal ganglia, thalami, prefrontal and lateral frontal cortex, and parietooccipital cortex.<sup>28</sup> However, perfusion patterns in PD patients are different in dominant symptoms and the early or late stage.<sup>29, 30</sup> Large variations in findings make it difficult to use brain perfusion SPECT to facilitate the differential diagnosis of PD.<sup>31</sup>

### DLB (Fig. 2)

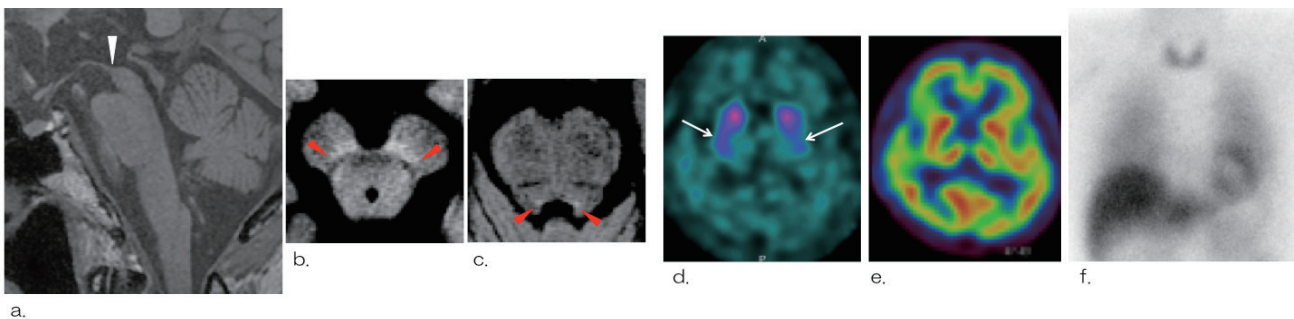
DLB is an atypical parkinsonian disorder recognized as the second most common cause of degenerative dementia in older individuals following AD. Conventional MR imaging is of little value for the diagnosis of DLB. MR imaging findings in patients with DLB are frequently



**Fig. 2.** Dementia with Lewy bodies in an 88-year-old male. (a) A T2-weighted MR image demonstrates marked atrophy of the medial temporal lobes including the hippocampus. (b, c) NmMRI shows decreased hyperintensity in the lateral part of the substantia nigra (arrowheads) and locus coeruleus (arrowheads). (d) Markedly decreased striatal DaT uptake (arrows) is observed. (e) Perfusion SPECT shows bilateral occipital hypoperfusion (arrowheads) that is frequently observed in DLB. (f) Markedly decreased myocardial MIBG uptake (arrows) is also observed. DaT, dopamine transporter; DLB, dementia with Lewy bodies; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; NmMRI, neuromelanin-sensitive MR imaging; SPECT, single photon emission computed tomography.



**Fig. 3.** Multiple system atrophy in a 64-year-old female. (a) A T2-weighted MR image demonstrates cruciform hyperintensity (arrow) in the pons, termed the “hot cross bun.” (b, c) NmMRI shows decreased hyperintensity in the substantia nigra (arrowheads) and locus coeruleus (arrowheads). (d) Markedly decreased striatal DaT uptake (arrows) is observed. (e) Perfusion SPECT shows marked hypoperfusion (arrowheads) in the pons and cerebellum. (f) Myocardial MIBG scintigraphy shows normal myocardial MIBG uptake. DaT, dopamine transporter; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; NmMRI, neuromelanin-sensitive MR imaging; SPECT, single photon emission computed tomography.



**Fig. 4.** Progressive supranuclear palsy in a 71-year-old male. (a) A sagittal T1-weighted MR image shows midbrain atrophy with a concave (arrowhead) upper surface (hummingbird sign) compatible with PSP. (b, c) Decreased hyperintensity in the lateral substantia nigra (arrowheads) and locus coeruleus (arrowheads) is observed on NmMRI. (d) Decreased DaT uptake in the bilateral putamina (arrows) is observed. (e) Perfusion SPECT shows normal perfusion in both basal ganglia. (f) Myocardial MIBG scintigraphy shows normal myocardial MIBG uptake. DaT, dopamine transporter; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; NmMRI, neuromelanin-sensitive MR imaging; PSP, progressive supranuclear palsy; SPECT, single photon emission computed tomography.

non-specific, with varying patterns of atrophy and white matter signal changes.<sup>21</sup> A pattern of generalized cortical atrophy with notably less atrophy in the hippocampus

than AD has been reported.<sup>32</sup> DTI shows diffusely increased mean diffusivity with specifically reduced fractional anisotropy in the parietooccipital white mat-

ter, pons, and left thalamus.<sup>33</sup> Although these findings are useful as a group study, it may be difficult to apply them to individual patients. On the other hand, NmMRI revealed a reduction in the hyperintense signal in the substantia nigra, which is useful for the diagnosis of nigrostriatal degeneration caused by a striatal dopamine deficiency.<sup>16</sup>

DaTSCAN demonstrates variable patterns of decreased dopaminergic activity in patients with DLB. These patterns are useful for differentiating DLB from AD, which demonstrates preserved dopaminergic activity.<sup>21</sup> However, it is not possible to distinguish DLB from other atypical parkinsonian disorders such as MSA, PSP, and CBD with DaTSCAN due to overlapping patterns.<sup>21</sup> On the other hand, MIBG myocardial scintigraphy is useful for differentiating Lewy body-related diseases from non-Lewy body diseases including MSA, PSP, CBD, AD, vascular dementia, and frontotemporal dementia.<sup>34</sup> MIBG myocardial scintigraphy has the potential to accurately diagnose Lewy body-related disease in its preclinical stages, which may be useful for evaluating disease-modifying and/or preventive interventions.<sup>34</sup>

Occipital hypometabolism is the most distinct finding in DLB relative to AD and healthy controls.<sup>35</sup> Reduced occipital metabolism and perfusion are supportive features in the 2005 consensus criteria for DLB.<sup>36</sup> Kantarci et al. reported a relationship between occipital hypometabolism and the frequency of visual hallucinations, which is one of the three core characteristics of DLB.<sup>37</sup> However, occipital hypometabolism and hypoperfusion are not always present in neuropathologically confirmed DLB.<sup>11, 38</sup> On the other hand, the posterior cingulate island sign, which reflects relatively preserved metabolism in the posterior cingulate region, is sensitive and specific for DLB and is useful for differentiating AD.<sup>39</sup>

### **MSA** (Fig. 3)

MSA consists of two forms: MSA-P – with predominant parkinsonism (80% of patients) and MSA-C – with predominant cerebellar ataxia (20% of patients), accompanied by dysautonomia in both subtypes.<sup>12</sup> These two clinical variants also differ in terms of brain areas involved in the pathological process – in MSA-C, neurodegeneration predominately affects the brainstem and cerebellum, while in MSA-P, the basal ganglia, particularly the putamen, are involved.<sup>11</sup> Typical MR imaging findings observed in MSA-P are: a hyperintense putaminal rim, putaminal atrophy and hypointensity, atrophy of and signal decreases in the globus pallidus, and infratentorial signal increase and atrophy. In MSA-C, the most characteristic changes are: atrophy of the mid-

dle cerebellar peduncle, dilatation of the 4th ventricle, atrophy of the pons, and an increased signal within the cerebellum, middle cerebellar peduncles, and pons.<sup>12</sup> These changes may produce cruciform T2 hyperintensity within the basis pontis, popularly referred to as the hot cross bun sign.<sup>21</sup>

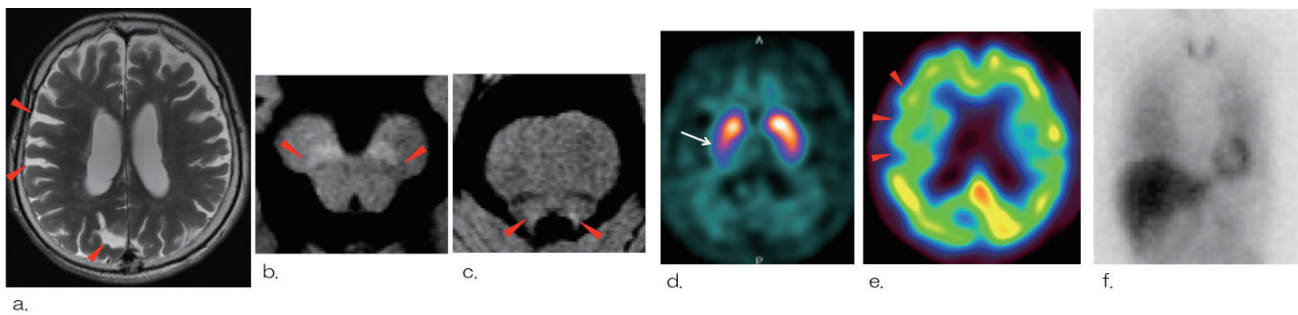
The presence of putaminal atrophy appears to help discriminate MSA from PD, whereas putaminal T2 hypointensity is a non-specific sign that may also be observed in PSP, Wilson's disease, neurodegeneration with brain iron accumulation, and other acquired conditions.<sup>21</sup> NmMRI revealed a reduction in the hyperintense signal in the substantia nigra, which is useful for the diagnosis of nigrostriatal degeneration caused by a striatal dopamine deficiency.<sup>16</sup>

DaTSCAN demonstrates reduced striatal dopaminergic activity with variable patterns, which may be symmetric or asymmetric and affect the putamen or caudate nucleus.<sup>21</sup> Although a reduction in myocardial MIBG may be present in some MSA patients, myocardial MIBG uptake is generally not reduced in MSA. Therefore, a high sensitivity of 90.2% and high specificity of 81.9% have been reported for differentiating PD from MSA.<sup>34</sup> Perfusion SPECT shows hypoperfusion in the pons and cerebellar hemisphere in MSA-C. Asymmetrical cerebellar hypoperfusion is common in patients with MSA-C.<sup>40</sup>

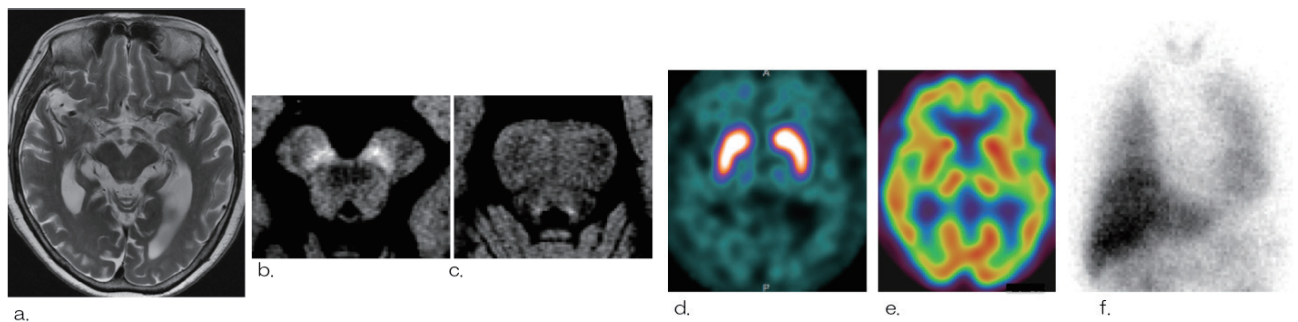
### **PSP** (Fig. 4)

Conventional MR imaging shows midbrain atrophy with relative preservation of the pons, which produces an appearance sometimes referred to as the “hummingbird sign” or “penguin sign” on the midsagittal plane, with the tegmentum representing the head with a long, thin beak, and the pons the body of the hummingbird or penguin.<sup>13,21</sup> Massey et al. reported that the hummingbird sign on the midsagittal plane with rostral midbrain atrophy and concavity was observed in 67% of pathologically confirmed PSP cases.<sup>41</sup> PSP has recently been recognized to comprise various clinical subtypes, except for typical cases (i.e., Richardson's syndrome).<sup>42</sup> Therefore, the lack of characteristic midbrain atrophy on MR imaging is expected. Additional findings include superior cerebellar peduncle atrophy and a stronger fluid-attenuated inversion recovery (FLAIR) signal, both of which have reasonably high sensitivity and specificity in distinguishing PSP from PD and MSA.<sup>21</sup> NmMRI also reveals a reduction in the hyperintense signal in the substantia nigra and is useful for atypical parkinsonian disorders.

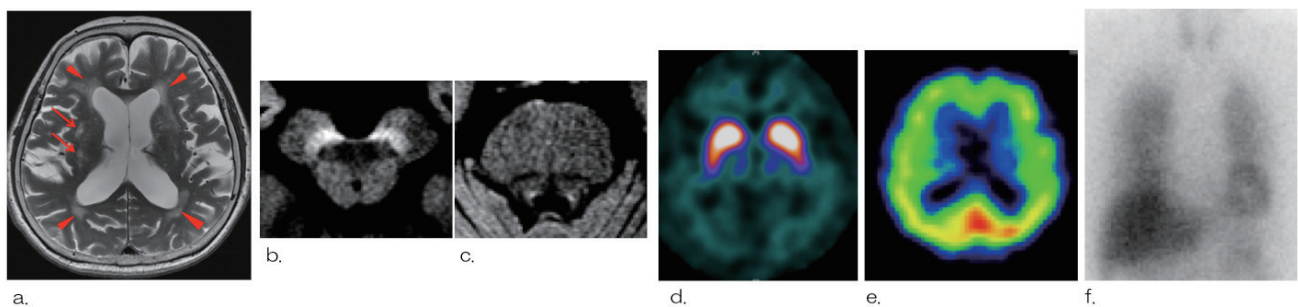
DaTSCAN shows reduced tracer uptake in the striatum. Striatal DaT is generally decreased more in PSP



**Fig. 5.** Corticobasal degeneration in a 79-year-old female. (a) A T2-weighted MR image demonstrates diffuse brain atrophy. Widening of the right frontal cortical sulci and parietooccipital sulcus are prominent (arrowheads). (b, c) NmMRI shows decreased hyperintensity in the lateral part of the substantia nigra (arrowheads) and locus coeruleus (arrowheads). (d) Slightly decreased striatal DaT uptakes (arrow) are observed in the right side. (e) Perfusion SPECT shows diffuse hypoperfusion of the cerebral cortex, particularly the right frontal lobe (arrowheads) (f) Myocardial MIBG uptake is preserved. DaT, dopamine transporter; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; NmMRI, neuromelanin-sensitive MR imaging; SPECT, single photon emission computed tomography.



**Fig. 6.** Essential tremor in an 87-year-old female. (a) A T2-weighted MR image demonstrates no definite abnormalities in the midbrain. (b, c) Hyperintense regions in the substantia nigra and locus coeruleus are preserved on NmMRI. (d) DaTSCAN shows normal DaT uptake in the bilateral striatum. (e) Perfusion SPECT shows normal perfusion in the cerebral cortices and basal ganglia. (f) Myocardial MIBG scintigraphy shows normal myocardial MIBG uptake. DaT, dopamine transporter; DaTSCAN, dopamine transporter SPECT; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; NmMRI, neuromelanin-sensitive MR imaging; SPECT, single photon emission computed tomography.



**Fig. 7.** Vascular parkinsonism in an 81-year-old female. (a) A T2-weighted MR image demonstrates small infarcts in the right basal ganglia (arrows) and diffuse white matter lesions (arrowheads). (b, c) Hyperintense regions in the substantia nigra and locus coeruleus are preserved on NmMRI. (d) DaTSCAN shows normal DaT uptake in the bilateral striatum. (e) Perfusion SPECT shows decreased hypoperfusion of the bilateral frontal cortices. (f) Myocardial MIBG scintigraphy shows normal myocardial MIBG uptake. DaT, dopamine transporter; DaTSCAN, dopamine transporter SPECT; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; NmMRI, neuromelanin-sensitive MR imaging; SPECT, single photon emission computed tomography.

than in MSA-P and PD with the uniform involvement of dopamine terminals in the caudate and putamen.<sup>22</sup> By exploiting the capability of perfusion SPECT to in-

vestigate regional cerebral blood flow and characteristic distribution to the medial frontal cortex of pathological alterations in PSP, Varrone et al. reported that evidence

of hypoperfusion in the anterior cingulate and medial frontal cortex may represent an additional feature to differentiate PSP from PD. MIBG myocardial scintigraphy is generally normal in PSP.<sup>22</sup> This technique is extremely useful for differentiating PSP from PD and DLB.

### **CBD** (Fig. 5)

In the early stages of disease, conventional MR imaging findings may be subtle, but abnormal. Asymmetric atrophy centered in the posterior frontal and parietal lobes and corpus callosum atrophy develop in a significant proportion of patients. There may also be associated atrophy of the ipsilateral cerebral peduncle without Wallerian degeneration of the corticospinal tract.<sup>13, 21</sup> However, Lee et al. reported using VBM by MR imaging that many patients with CBD fall within the range of asymmetry observed in healthy controls.<sup>43</sup> Therefore, it is important to note that CBD often has a clinically and anatomically symmetric presentation, although asymmetry has been stressed as a core feature of CBD. T2-weighted and FLAIR images may reveal subcortical white matter hyperintensity in the atrophic frontoparietal sulci, presumably reflecting neuronal degeneration.<sup>21, 44</sup> NmMRI reveals a reduction in the hyperintense signal in the substantia nigra, reflecting nigrostriatal degeneration caused by a striatal dopamine deficiency.

DaTSCAN demonstrates variable decreased putaminal activity that, similar to atrophy in MR imaging and hypometabolism in <sup>18</sup>F-fluorodeoxyglucose (FDG) PET, is often asymmetric and contralateral to the affected side.<sup>21</sup> This frequently manifests as left-sided cerebral hypometabolism in the cortex of right-sided symptoms.<sup>13</sup> A perfusion SPECT study showed asymmetric hypoperfusion in the frontoparietal lobes and basal ganglia.<sup>22</sup> In general, MIBG myocardial scintigraphy is normal in CBD.<sup>22</sup>

### **ET** (Fig. 6)

Typical ET cases may be easily diagnosed and distinguished from PD. However, the clinical differentiation between these conditions may be challenging, and considerable overlap has been reported in clinical features, particularly in the early stages of the disease.<sup>45</sup>

Several MR imaging studies have investigated anatomical and functional brain alterations in ET patients, and some pathological studies recently provided evidence of structural brain changes in this disease that may be associated with neurodegeneration.<sup>45</sup> On DTI, microstructural changes with neurodegeneration were detected in the dentate nucleus and superior cerebellar peduncle of patients with familial ET.<sup>46</sup> On NmMRI, neuromelanin in the substantia nigra was not signifi-

cantly lower than that in the healthy control group in ET, whereas PD patients, even at the time of the clinical diagnosis, exhibited a significant reduction in the substantia nigra, which was more pronounced laterally in accordance with pathological changes. Therefore, NmMRI may become a useful diagnostic tool for the differentiation of ET from PD in very early clinical stages.<sup>45</sup>

DaTSCAN discriminates ET and PD because patients with ET consistently and effectively have normal striatal DaT binding. In a meta-analysis of the diagnostic differentiation of ET and PD using DaTSCAN, the study with the lowest sensitivity and specificity reported percentages of 80% and 95%, respectively.<sup>27,47</sup> Regarding MIBG myocardial scintigraphy, Lee et al. reported that myocardial MIBG uptake in patients with ET was within the normal range and clearly distinguishes them from patients with PD.<sup>48</sup>

### **VP** (Fig. 7)

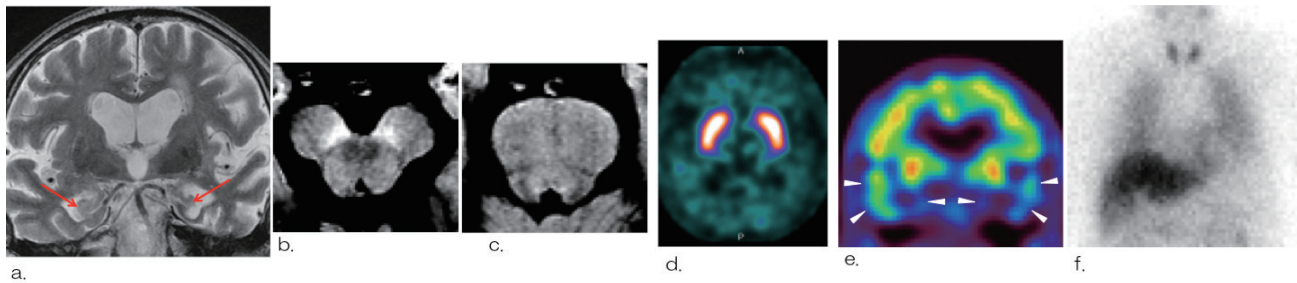
As a basic requirement for VP, Zijlmans et al. concluded that vascular disease may *per se* be a cause of parkinsonism in the absence of alternative or co-existing pathological lesions linked with neurodegenerative disease.<sup>49</sup> However, a clinical diagnosis of VP is still difficult because vascular lesions are a common incidental finding in pathologically confirmed PD. As MR imaging is important for the diagnosis of VP, MR imaging needs to play a complementary role in the diagnosis of VP.

Functional imaging is helpful for differentiating between parkinsonian syndromes. In the presence of vascular lesions on CT/MR imaging (e.g., a “punched out” lesion characteristic of an infarct or the diffuse white matter disease of ischemia), normal DaTSCAN findings are diagnostic of VP.<sup>27, 47</sup> A meta-analysis of the diagnostic differentiation of PD and VP using DaTSCAN demonstrated a sensitivity of 80%–100% and specificity of 73%–100%.<sup>47</sup> Regarding MIBG myocardial scintigraphy, Navarro-Otano et al. demonstrated from the evaluation of a relatively small sample size that this method was useful for differentiating between VP and PD when the findings of DaTSCAN were confusing.<sup>50</sup>

### **AD** (Fig. 8)

AD is the most common cause of dementia. AD is generally not included in the differential diagnosis of parkinsonism. However, differentiating between AD and DLB or Parkinson’s disease dementia is challenging if dementia precedes motor symptoms. In some cases, the clinical differentiation of patients with AD from those with DLB may be difficult because of overlapping clinical and pathological features.<sup>6</sup>





**Fig. 8.** Alzheimer's disease in an 80-year-old male. (a) A T2-weighted MR image demonstrates marked atrophy of the bilateral temporal lobes including the hippocampus (arrows). (b, c) Hyperintense regions in the substantia nigra and locus coeruleus are preserved on NmMRI. (d) DaTSCAN shows normal DaT uptake in the bilateral striatum. (e) Perfusion SPECT shows marked hypoperfusion in the bilateral temporal lobes (arrowheads). (f) There are no abnormalities on myocardial MIBG scintigraphy. DaT, dopamine transporter; DaTSCAN, dopamine transporter SPECT; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; NmMRI, neuromelanin-sensitive MR imaging; SPECT, single photon emission computed tomography.

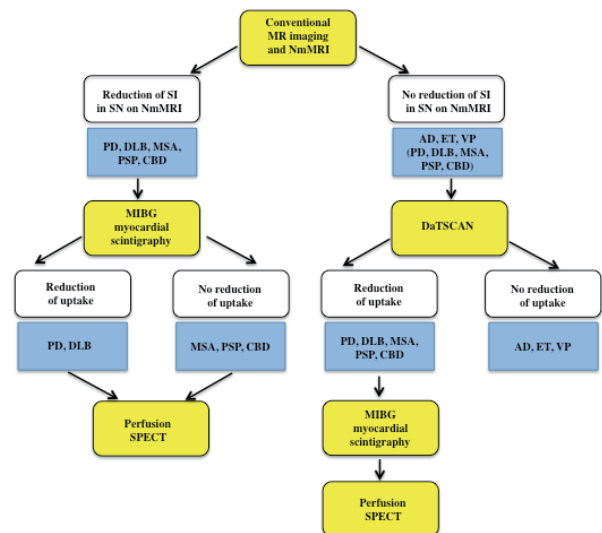
Conventional MR imaging shows focal volume loss classically starting in the entorhinal cortex, involving the medial temporal lobe and hippocampus, as well as the parietal lobe in AD.<sup>51</sup> NmMRI shows no reduction in signal intensity in the substantia nigra in AD, while a signal reduction in the substantia nigra is prominent in patients with PD and DLB. These findings are useful for the differentiation of AD from DLB.<sup>23, 24</sup>

Hypometabolism and hypoperfusion on FDG PET and perfusion SPECT may be detected before the onset of clinical symptoms, showing a typical topographic pattern: the posterior cingulate-precuneus region is affected first, followed by the lateral temporoparietal region.  $^{11}\text{C}$ -PIB PET shows increased cortical uptake with the highest retention in the frontal, cingulate, precuneus, striatum, parietal and lateral temporal cortex.<sup>51, 52</sup>

Recent studies have indicated that MIBG myocardial scintigraphy provides diagnostic information that is useful for differentiating DLB from AD.<sup>6</sup> Moreover, the combination of DaTSCAN and MIBG myocardial scintigraphy may provide a powerful differential diagnostic tool when it is difficult to differentiate patients with DLB from those with AD using DaTSCAN or MIBG myocardial scintigraphy alone.<sup>6</sup>

### DIFFERENTIATION OF PD AND ITS RELATED DISEASES BY NEUROIMAGING (Fig. 9)

Although the gold standard for the diagnosis of PD and its related neurodegenerative diseases is a postmortem neuropathological examination<sup>27</sup>, the diagnosis of these diseases is still largely based on the correct identification of their clinical features.<sup>1</sup> In spite of advances in clinically available anatomical and functional neuroimaging, these neuroimaging findings in the consensus guidelines for the diagnosis are extremely limited. However, recent



**Fig. 9.** A diagnostic algorithm using neuroimaging for PD and its related diseases. AD, Alzheimer's disease; CBD, corticobasal degeneration; DaTSCAN, dopamine transporter SPECT; DLB, dementia with Lewy bodies; ET, essential tremor; MIBG,  $^{123}\text{I}$ -metaiodobenzylguanidine; MSA, multiple system atrophy; NmMRI, neuromelanin-sensitive MR imaging; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SI, signal intensity; SN, substantia nigra; SPECT, single photon emission computed tomography; VP, vascular parkinsonism.

advances in neuroimaging may highlight the need for radiologists to become familiar with these imaging findings.

MR imaging is easily available in most hospitals. SPECT systems are generally less expensive and more widely available in most hospitals than PET instruments. Therefore, we provide a practical diagnostic approach for PD and its related diseases using MR imaging and

MIBG myocardial scintigraphy and SPECT in this review. However, we must get the attention of readers in the following respects in the evaluation of molecular imaging such as SPECT. Several therapeutic drugs, symptom duration, and patient age can affect the uptake of radiotracers in the target organs.<sup>53-55</sup> For the quantitative evaluation of uptake of radiotracer, it is important to recognize the difference between the gamma camera systems including collimators.

With the above in mind, first, conventional MR imaging and NmMRI should be applied to the patients with movement disorders and/or dementia. Second, DaTSCAN or MIBG myocardial scintigraphy should be selected according to these MR imaging findings. Moreover, a combination of these neuroimaging methods is a useful and practical approach for the differential diagnosis and confirmation of PD and its related diseases. However, we also stress that we should select the neuroimaging modality easily available in your hospital with knowledge of the neuroimaging findings mentioned above in mind for its differentiation.

## CONCLUSION

A combination of clinical features with MR imaging and MIBG myocardial scintigraphy and/or DaTSCAN is recommended for optimization of the diagnostic algorithm in PD and its related diseases.

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