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LEADING TOPIC

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Neuroimaging in Parkinson's Disease: necessity or exaggeration?

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ABSTRACT

Introduction. Neuroimaging plays an increasingly important role in the diagnosis of parkinsonian syndromes.

Aim of the study. In this paper, the authors elaborate on the necessity of using magnetic resonance imaging (MRI) in Parkinson's Disease (PD) and its potential role in differential diagnosis versus other neurodegenerative parkinsonian syndromes such as dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy and corticobasal syndrome.

State of the art. The currently known characteristic abnormalities are listed and tabulated, current recommendations are summarised and sample images are provided. As routine MRI scanning in PD remains controversial, the authors' aim is to show the pros and cons in clinical practice. Additionally, the rationale for functional imaging examination, including [^{123}I]-FP-CIT SPECT (DaTSCAN) and [99mTc]- HMPAO-SPECT, [^{18}F]-FDG-PET, [^{123}I]-mIBG-SPECT is discussed.

Clinical vignette. This paper is accompanied by two illustrative clinical cases in which neuroimaging studies played a key role in diagnosis and further management.

Conclusions. Neuroimaging can be helpful in differentiating PD from both atypical and symptomatic parkinsonism. Nevertheless, extensive neurological assessment in a majority of PD cases is sufficient to make a diagnosis. A network of specialists in movement disorders should be established in order to enable better, faster and more precise diagnosis of parkinsonism.

Key words. Parkinson's Disease, atypical parkinsonism, neuroimaging, DaTSCAN, magnetic resonance imaging, single photon emission computed tomography

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Introduction

Parkinson's Disease (PD) is primarily diagnosed according to the current Movement Disorders Society (MDS-2015) based on a neurological examination. Magnetic resonance imaging (MRI) is not recommended criteria in the routine diagnosis of typical levodopa (LD)-responsive PD [1]. Similarly, the widely available dopamine transporter single-photon emission

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computed tomography (SPECT) using [^{123}I]-FP-CIT (ioflupane), trade name: DaTSCAN should not be used routinely to confirm the diagnosis of PD, and officially is licensed only for the differential diagnosis of PD and Essential Tremor (ET) [1–3]. Nevertheless, there is a substantial number of studies looking for specific MRI signs that may be helpful in a diagnosis of PD and differentiate PD from atypical parkinsonian syndromes (APS) such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), cortico-basal syndrome (CBS) or dementia with Lewy bodies (DLB) and symptomatic parkinsonism. Therefore, in 2013, the European Federation of Neurological Societies (curently — European Academy of Neurology), recommended conventional MRI and diffusion-weighted imaging at 1.5T as neuroimaging tools to support a diagnosis of MSA or PSP versus PD [4].

The aim of this paper is to discuss whether conventional MRI, DaTSCAN and other functional neuroimaging modalities may be helpful in clinical practice when diagnosing parkinsonian syndromes, and how to avoid both unnecessary examinations and misdiagnosis. We will analyse the rationales for making these decisions. This paper uses the current diagnostic criteria and is based on a literature review, but it also reflects the personal views and approaches of the authors.

Clinical reasoning

PD is a neurodegenerative disorder characterised by both motor and non-motor symptoms that appear mostly at middle and late stages (dysautonomia, cognitive decline, depression, sleep disorders, hallucinations and delusions) and thus are not helpful in making a diagnosis in the early stages [5]. The diagnosis of PD, according to MDS-PD criteria, is primarily based on a neurological examination [1]. The essential criterion is the presence of bradykinesia and at least one of either rest tremor or rigidity. Further steps to diagnose idiopathic PD involve determining whether absolute exclusion criteria (including atypical symptoms such as early dementia, gaze palsy and cerebellar and pyramidal symptoms) and red flags are absent, and whether at least two supporting criteria are present. The utility of the LD challenge test remains controversial [4]. Therefore the only way to detect if LD is effective is to up-titrate to an adequate dose of 600 mg/day or more (up to 1,000 mg/day) within three months [1, 2]. A good or very good response can confirm a proper diagnosis of PD. Nevertheless, even in specialised movement disorders centres, up to 26% of patients initially diagnosed with PD are reclassified at follow-up [6–8].

Neuroimaging studies are not obligatory for diagnosing typical cases of PD [1]. However, from a clinical perspective, they should be requested if atypical symptoms (early dementia, dysautonomia, cerebellar symptoms, pyramidal signs, wide-base gait and falls, early orthostatic hypotonia and urinary incontinence) or an atypical clinical course (rapid or stepwise deterioration) with no or suboptimal LD responsiveness, are present. In some cases, this may enable identification of a potentially treatable condition (e.g. normal pressure hydrocephalus [NPH], Wilson's Disease) or the introduction of a secondary prophylactic (vascular parkinsonism [VaP]).

Nevertheless, these conditions are rare and present distinctive clinical features, usually not typical parkinsonian syndrome alone. In NPH, early gait problems, with rather wide-base gait (narrow in PD), is present, followed by dementia and urinary incontinence. Wilson's Disease may progress faster, with prominent dystonic postures and hepatic lesions and should be thoroughly diagnosed using a combination of methods, including biochemical (serum ceruloplasmin; serum and urine copper) and ophthalmological (Kayser-Fleisher ring) examinations; genetic testing; and neuroimaging with MRI or transcranial ultrasonography [9–11]. Predominant gait problems are also typical for VaP, presenting as so-called lower body parkinsonism (of note: true VaP due to vascular lesions within nigrostriatal pathways is very rare) [9].

The differential diagnosis of PD and ET can be troublesome. The proposed MDS definition of ET requires at least a three-year history of tremor, excluding isolated head and voice tremors. A three-year history would reduce the odds of the subsequent development of other neurological signs (e.g. dystonia, parkinsonism or ataxia) [12]. From clinical practice, it is known that ET may present with asymmetric upper limb tremor – postural, kinetic and even at rest – with a family history and alcohol response in approximately 50% of patients. In contrast, tremor in PD may also be postural (typically with a delay, called re-emergent tremor, which differentiates it from classical ET). However, rest tremor combined with parkinsonism is usually asymmetric and commonly unilateral at onset and is known as classical parkinsonian rest tremor [12]. Clinical experience is required to make the distinction from ET (e.g. re-emergent tremor in PD), and one should also be aware of the possible combination of ET and PD.

Atypical ET, with a rest tremor and asymmetrical presentation, or an atypical parkinsonian tremor — called type II or III in the classification — with postural and/or kinetic components, may also be controversial [13]. A tremor evolving over a long period (sometimes known as benign tremulous parkinsonism) may cause problems with PD diagnosis in the early stages. The lack of responsiveness of PD tremor to LD (in approximately 30% of PD patients) makes differential diagnosis difficult in the early stages when other clinical features such as bradykinesia or rigidity are less pronounced. Therefore, when initiating LD treatment, one should pay more attention to improvement of bradykinesia, rigidity and gait than of tremor. Propranolol may improve both parkinsonian tremor and ET and thus may cause confusion in cases with rest tremor and other mild parkinsonian features.

Derived from the ELLDOPA study, a new category of patients was recognized. These are called SWEDDs (subjects without evidence of dopamine depletion), who had 'mild' parkinsonian features and were included into the study as patients fulfilling the PD diagnostic criteria [14]. Since then,

it has been found that 4–15% of patients originally diagnosed as PD do not have dopaminergic deficits in functional neuroimaging [15, 16]. Long-term observation has shown no PD symptoms in the majority of SWEDD cases, which was consistent with DaTSCAN imaging [17]. This was also recently supported by a study by Suwijn et al. in which a panel of six neurologists in training (NT), six general neurologists (GN), and six movement disorder experts (MDE) received a batch of 10 videos consisting of SWEDD subjects and a random sample of patients with abnormal DaTSCAN scans. The value of clinical signs in identifying patients was found to be poor (low intraclass correlation coefficients). The worst clinical assessments were made by GNs (33.3%) and NTs (50%), and the best by MDEs (66.7%) [18]. However, this actually confirms the necessity of training in clinical assessment of parkinsonism rather than performing obligatory DaTSCAN at early PD stage.

If neuroimaging is necessary, MRI is generally preferred over computer tomography (CT) due to the better tissue contrast resolution and sensitivity unless contraindicated [19] (e.g. cardiac implantable electronic devices, metallic intraocular foreign bodies, neurostimulation systems, metallic implants depending on their type and the strength of magnetic field). Although the spatial resolution of MRI is lower compared to CT it can be improved by the application of high-field (3T) and ultra-high-field (7T) MRI or by three-dimensional sequences with higher signal-to-noise ratio. Therefore, techniques sensitive to the presence of iron or neuromelanin at 3T or 7T MRI increase specificity of MRI in the diagnostics of parkinsonism.

Dopamine transporter single-photon emission CT (SPECT) [123I]- FP-CIT (ioflupane), trade name DaTSCAN, may be an option for detecting the integrity of the presynaptic dopamine system (nigrostriatal pathways). This radiotracer is officially licensed for differentiating between PD and ET and between Alzheimer's Disease (AD) and DLB. In PD and DLB, the nigrostriatal denervation results in a reduction in DaTSCAN uptake, and therefore these entities cannot be differentiated [20, 21].

Magnetic resonance imaging

In the authors' opinion, neuroimaging should always be performed at the onset of parkinsonian symptoms to exclude other causes of symptoms. Illustratively, the first link between parkinsonism and the substantia nigra (SN) was made by Paul Blocq and Georges Marinesco from the Charcot group, who discovered during the post mortem of a patient with a clinical diagnosis of tuberculosis and unilateral rest tremor, an encapsulated tumour confined to the SN, contralateral to the affected side, supporting the conclusion that tremor in this case resulted from a midbrain lesion [22].

Clinical vignette 1

The situation in which MRI can give surprising findings may be illustrated by the case of a 65-year-old woman who presented with rest tremor of the right hand which had lasted for several months, and bradykinesia, also on the right. Her GP had made a diagnosis of PD and started LD treatment with no effect (although the daily dose was relatively small at 400 mg). At the neurological examination, she presented along with parkinsonism and pyramidal signs on the right side. The MRI revealed a tumour of the pituitary gland with significant dilatation of the left ventricle. The removal of the tumour resulted in the disappearance of the hemi-parkinsonism. The delayed diagnostic process with LD challenge lasting nearly three months could have resulted in a fatal outcome, but the red flag of pyramidal signs was present and should have suggested symptomatic parkinsonism.

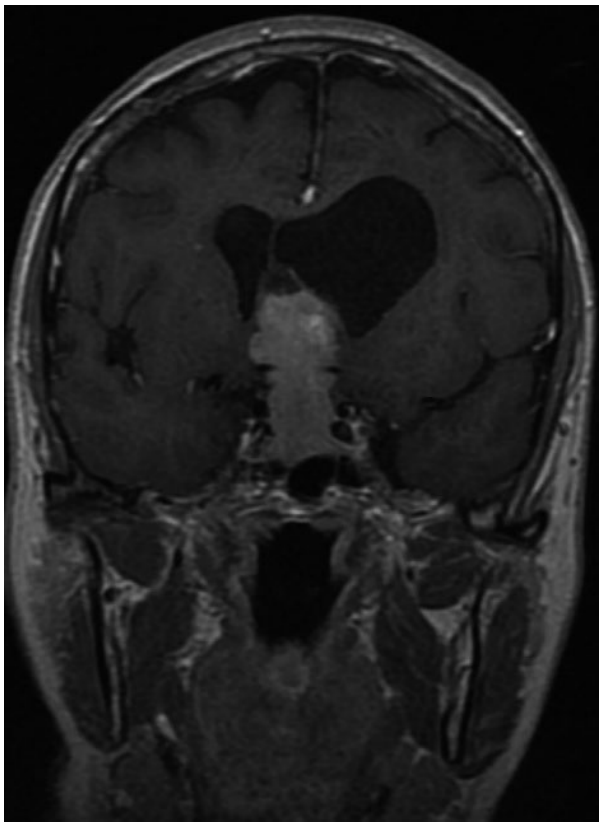

Figure 1. MRI image of pituitary gland tumour with asymmetric, contralateral parkinsonian syndrome

The role of structural 1.5T MR imaging in patients with idiopathic PD is so far questionable because of the lack of disease-specific signs [4] and according to the National Institute for Health and Care Excellence (NICE) guidelines should not be used to diagnose PD [23]. However, in clinical practice, brain MRI is usually performed at least once in the course of the disease, although some experts suggest performing a brain MRI only in patients with atypical features that suggest atypical or symptomatic parkinsonism [19]. Additionally, brain MRI plays an important role in excluding treatable causes of parkinsonism (as in clinical vignette 1), which should never be missed.

Cerebrovascular damage that can be seen on MRI may also be responsible for parkinsonian syndrome (mostly gait

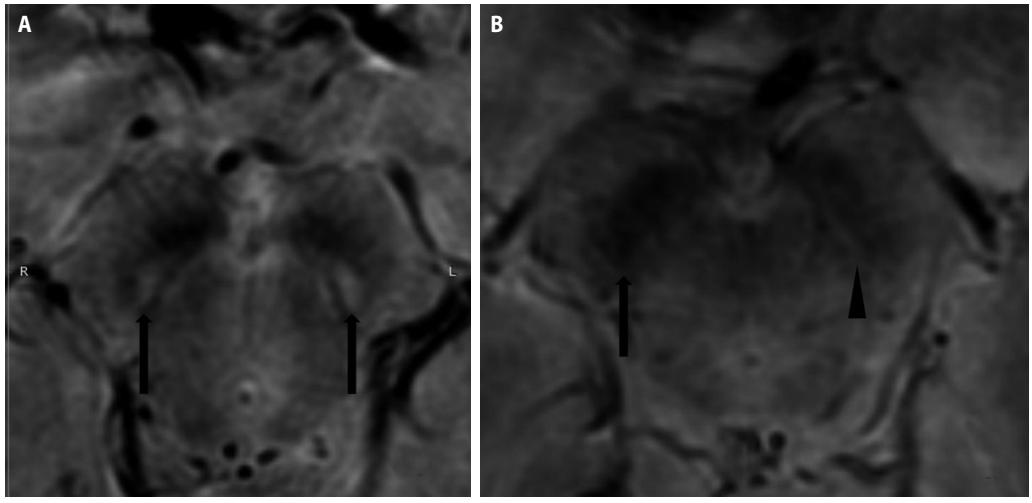

Figure 2. MRI, axial plane, high-resolution SWI. **A.** Bilateral DNH (arrows) — normal 'swallow-tail' sign, indicating healthy subject; **B.** Lack of DNH on right (arrow) and small, hardly visible nigrosome-1 on left (arrowhead), indicating PD

problems), but one should be aware that concurrent vascular lesions are relatively common in patients with PD or they may indicate so-called mixed neurodegenerative parkinsonism and cerebrovascular disease [24]. Lesions in the striatum may also cause reduced dopamine transporter uptake on DaTSCAN, and a combination of imaging findings from these two methods may be useful [24]. There are also some characteristics visible on MRI that are suggestive of other causes of parkinsonism, including iron storage disorders [25] Wilson's Disease [26] or manganese-induced parkinsonism [27].

Based on recent advances in MRI technology, new techniques using high-field (3T) and ultra-high-field (7T) MRI (nigrosome-1 imaging, neuromelanin sensitive MRI) [28] can add value to the diagnosis of PD and APS. Techniques such as diffusion-weighted imaging [DWI], diffusion tensor imaging [DTI], arterial spin labelling perfusion [ASL], functional MRI, which can also be performed on 1.5T MRI scanners, are based on group-wise comparisons, however cannot be used in the diagnostic work-up of individual patients, because of a lack of validated diagnostic criteria [19].

Currently, the most promising MRI marker is the swallow-tail sign (or dorsal nigral hyperintensity [DNH]), which is a focus of increased signal intensity in the hypointense dorsolateral substantia nigra [SN], consistent with the location of nigrosome-1 (N-1), the largest subgroup of five calbindin-poor clusters rich with dopaminergic neurons [29, 30] (Fig. 2). The nigral dopaminergic cells loss in the idiopathic PD starts and dominate in N-1, with subsequent increase of iron deposition, which results in loss of DNH [28]. The swallow-tail sign can be found bilaterally in almost all healthy controls on specific high-resolution iron-sensitive sequences (susceptibility-weighted imaging [SWI]) at 3T or 7T MRI, but only exceptionally at 1.5T MRI, which limits this method in everyday practice. The absence or poor visualisation of N-1 unilaterally or bilaterally (lack of a swallow-tail sign) was present in patients with PD with a sensitivity of 98.5%, specificity of 93.6%, positive predictive value (PPV) of 94.3% and negative predictive value (NPP) of 98.3% [31]. Additionally, there was a significant correlation between clinical symptoms and corresponding poor visualisation of N-1. According to a recent meta-analysis, the overall sensitivity and specificity of N-1 imaging on 3T MRI was comparable to that of 7T MRI, and both exceeded 94% [30]. However, poor visualisation of N-1 may also be caused by inappropriate scanning techniques (acquisition plane, slice thickness, parameters and the type of iron-sensitive sequence used) and/or technical artifacts, especially those caused by movement or magnetic field distortions [32]. Visual rating of DNH is subjective and observer-dependent, and in this regard the experience of the radiologist is essential. Therefore, there is a clear need for reproducible and standardised MR protocols as well as a systematic evaluation of the N-1 visibility [33].

There are some promising results concerning the presence of swallow-tail sign in patients with early stage PD. DNH was found abnormal at 3T MRI in patients with early PD (H&Y 1–2) with disease duration of less than 12 months, with the diagnostic accuracy of 94.6% and the side of the more affected N-1 was in concordance with clinical laterality, and additionally DaT deficiency and PD was confirmed by 18F-FP-CIT PET [34]. The absence of DNH on MRI with significantly lower putaminal dopaminergic activity on DaTSCAN was also noticed in a quarter to two-thirds of patients with idiopathic rapid eye movement sleep behaviour disorder (RBD) [35, 36]. These findings however need further investigation. The utility of swallow-tail sign in a diagnosis of neurodegeneration has been supported by studies that compared MRI to DaTSCAN/SPECT, with good concordance between visualisation of N-1 on MRI and the function of presynaptic dopaminergic system on DaTSCAN [37, 38]. Additionally, SWI and N-1 correlates well with DaTSCAN, with a concordance rate

Table 1. Radiological features of brain MRI in most common atypical parkinsonian disorders

Multiple System Atrophy [46–48, 82]	Progressive SupranuclearPalsy [47, 48, 55, 58–61]	Dementia with Lewy Body [83, 84]	Corticobasal syndrome/ /degeneration [85]
MSA-P: reduced putamen volume, low signal in T2WI and SWI (T2*GRE) of putamen, putaminal rim sign in 1.5T MRI **MSA-C:** hot-cross bun sign, MCP atrophy, cerebellar atrophy, dilatation of 4th ventricle, increased SI T2 of MCP, cerebellum	**Midbrain atrophy:** hummingbird or penguin sign, Mickey Mouse sign (axial scans), morning glory sign (axial scans), midbrain area < 70 mm^2, decrease of AP midbrain diameter on sagittal scans < 9.35, reduction of midbrain-pons index < 0.12 (< 0.15), normal approximately 0.24, SCP atrophy, MRPI ≥ 13.55, callosal atrophy andmild cortical frontal atrophy	Generalised decrease in cerebral volume most marked in frontal lobes and parieto-temporal regions, mesial temporal lobe and hippocampi remain relatively normal	A symmetric cortical atrophy of superior parietal lobe (most common), peri-Rolandic gyri, superior frontal gyri bilateral atrophy of basal ganglia, atrophy of corpus callosum

of 86.2% [39, 40]. These results indicate that N-1 imaging can act as a potential screening tool in uncertain cases before the DaTSCAN [41].

However, similarly to PD, the DNH is also absent in most [39] or all [42] patients with APS, resulting in similar inability to distinguish those conditions with DaTSCAN imaging. Although one study showed that nigrosome-1 was bilaterally present in patients with MSA, this was not confirmed with DaTSCAN [43]. Very high NPP allows the exclusion of PD and APS in patients with a bilaterally normal swallow-tail sign with a confidence of nearly 100% [42, 38]. In contrast, normal bilateral DNH has been seen in patients with ET [44], drug-induced parkinsonism [41], VaP [45], AD and frontotemporal dementia.

This is therefore a potential biomarker for differentiating these conditions from neurodegenerative parkinsonism [30, 40].

MRI imaging may be helpful in diagnosing APS including PSP, MSA or CBS. The most common APS presents some distinctive, but not specific, MRI features, as set out in Table 1. These features are usually seen in the advanced stages of the disease, so the initial diagnostic accuracy of MRI (in the early stages) is limited [28].

Two variants can be distinguished in the clinical spectrum of MSA: MSA with predominant cerebellar signs (MSA-C), with neuropathology located predominantly in the brainstem and cerebellum, and MSA with parkinsonism (MSA-P), with primary involvement of basal ganglia, particularly the putamen [46].

In MSA-P, the most striking MRI feature at 1.5T is reduced volume of the posterior putamenwith low signal intensity on T2WI and SWI (or T2*GRE) relative to the globus pallidus and red nucleus. This can be accompanied by a marginal slit-like T2 hyperintensity along the postero-lateral part of the putamen ('putaminal rim' sign). Of note, this 'putaminal rim sign' should not be confused with a thinner rim along the entire lateral margin of the putamen seen in healthy subjects at 3T MRI [47, 48]. A similar hyperintense rim has been observed at 1.5T on axial T2W images in up to 38.5% of healthy subjects, but it occupied the full length or anterior half of the lateral margin of the putamen, with normal signal intensity of putamen and without evidence of atrophy [49]. In the assessment of putaminal abnormalities in MSA, weighted imaging is considered to be superior to T2WI and T2*GRE. Additionally, due to the higher sensitivity of iron, putaminal abnormalities in patients with MSA-P can differ at 3T MRI and 1.5T MRI. Therefore, the signal changes in the putamen on T2W imaging that are seen at 3T MRI are not specific for MSA-P, and can be also present in PD patients and healthy individuals [50].

Supratentorial abnormalities are observed more often and earlier in the course of MSA-P than in MSA-C, and demonstrate high specificity for differentiating MSA from PD, while putaminal changes are inadequate for distinguishing MSA from other forms of APS [47]. Infratentorial abnormalities, which are seen earlier and are more prominent in MSA-C, include atrophy of the cerebellum, pons and middle cerebellar peduncle (MCP), with increased signal intensity on T2WI and FLAIR along with a suggestive pattern of hyperintensity in the pons known as the 'hot cross bun' sign, [4, 19, 46, 47] (Fig. 2). This sign, however, can also be found in non-neurodegenerative parkinsonism and in spinocerebellar ataxia [47, 51].

Watanabe et al. reported that approximately 60% of patients with MSA-P, and 40% with MSA-C, showed no evidence of putaminal or infratentorial changes two years after disease onset [51, 52]. A longitudinal study with 3T MRI showed that about 20% of patients diagnosed with probable MSA-P had no abnormalities on initial MRI [53]. One should therefore remember that, in the absence of these MRI signs, APS still cannot be excluded, especially in the early course of the disease [19]. A follow-up neurological examination, along with MRI studies, is recommended.

In PSP, the most prominent feature on a brain MRI is atrophy of the midbrain, although not present in all patients, especially in the early phase of the disease. Midbrain atrophy depends also on the PSP phenotype, and is most characteristic

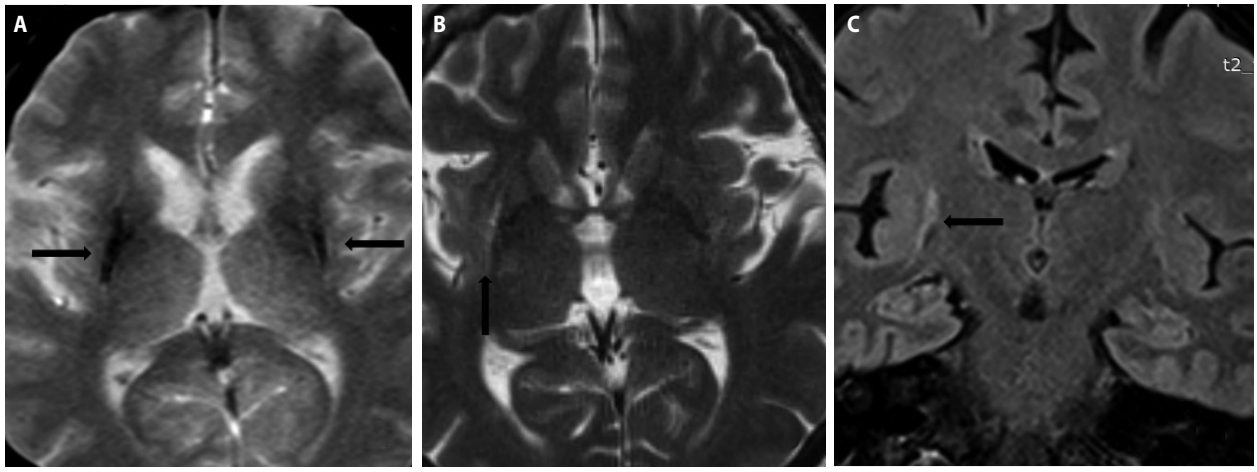

Figure 3. MRI, MSA with parkinsonism. **A.** Axial, T2*GRE; bilateral putaminal hypointensity and atrophy with loss of normal convex outer margin of putamen (arrows) — right putamen more affected than left; **B.** Axial T2WI; **C.** Coronal FLAIR — 'slit-like' hyperintensity along lateral margin of right putamen (arrows)

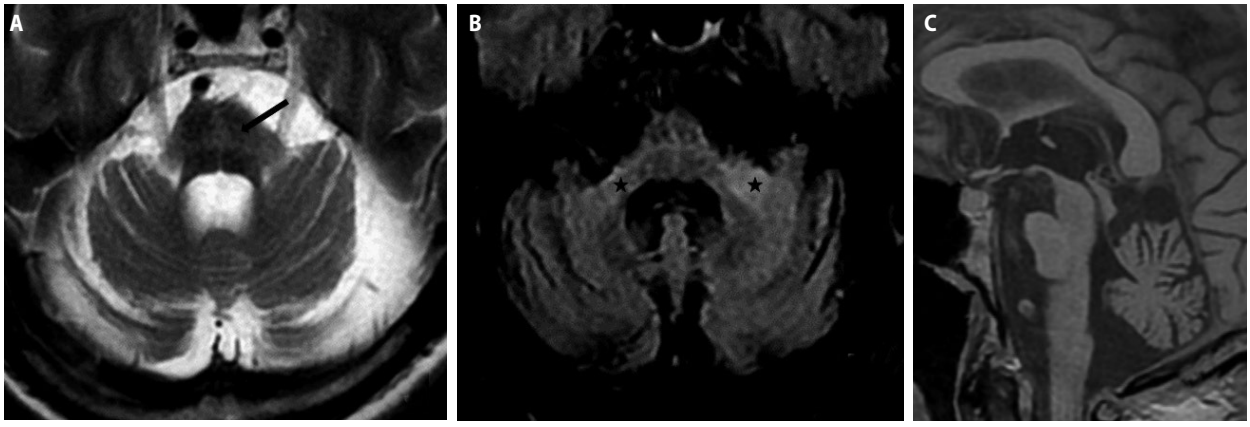

Figure 4. MRI, MSA-C. **A.** Axial T2WI; crossed hyperintensity in pons — 'hot cross bun' sign (arrow), enlarged 4th ventricle; **B.** Axial FLAIR; hot cross bun sign, marked atrophy of MCPs with hyperintense signal (stars); **C.** Sagittal plane, T1WI; atrophy of pons, normal midbrain size

for Richardson's Syndrome (PSP-RS) [54]. The midbrain profile on sagittal scans and the small area of the midbrain results in a so-called 'hummingbird' or 'penguin' sign. The 'Mickey Mouse' sign can be seen on the axial scan due to the decrease in the anteroposterior dimension of the midbrain at the level of the superior colliculi. Another symptom resulting from the loss of the lateral convex margin of the tegmentum of the midbrain is the 'morning glory' sign. This, together with the hummingbird sign, has low sensitivity, especially in the early disease stages, but high specificity of 99.5% and a positive predictive value of 96.1% for a diagnosis of PSP [55] (Fig. 4 A, B, C). Putaminal atrophy and hypointensity on SWI (or T2*GRE) can also be present [48].

Brainstem measurements are helpful in the differential diagnosis of PSP from PD and MSA, although the values of morphometric parameters differ between studies [56, 57]. The AP diameter of the midbrain is easy to measure in the sagittal plane on T1WI. Highly suggestive for PSP is perpendicular to the long axis of the midbrain without quadrigeminal plate, of less than 9.35 mm [58] and a midbrain area reduction to below 70 mm^2 (50% of the normal values) [59]. A ratio of the AP diameter of the midbrain to the AP diameter of the pons of less than 0.52 was found to have a specificity of 100% in discriminating PSP from non-PSP patients [58]. Additionally, the ratio of the midbrain area to the pons area (M area/ /P area) was reported to be reduced to ≤ 0.12 to ≤ 0.15 (normal: 0.24) [60]. Reported cut-offs for the AP midbrain diameter range from 9.35 mm to 14.85 mm, depending on the plane of assessment or on whether the midbrain was measured with or without midbrain tegmentum [56, 58, 59, 61]. Superior cerebellar peduncles (SCPs) are also atrophic in PSP, with relative sparing of the MCPs and pons. Measurements of the SCP, MCP, pons area and midbrain area allow the calculation of the MRI parkinsonism index (MRPI), wherein a value of ≥13.55 or

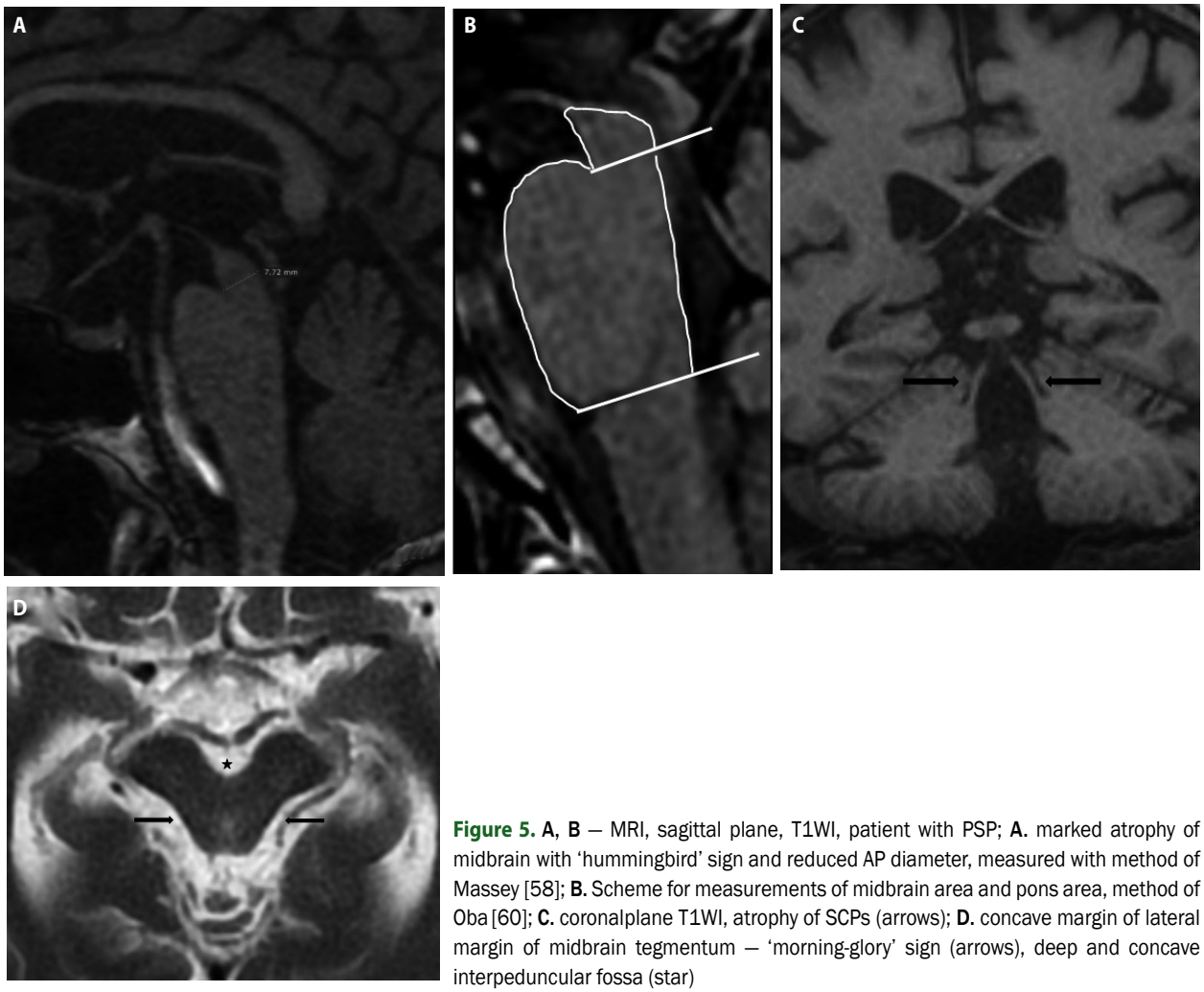

Figure 5. **A, B** — MRI, sagittal plane, T1WI, patient with PSP; **A.** marked atrophy of midbrain with 'hummingbird' sign and reduced AP diameter, measured with method of Massey [58]; **B.** Scheme for measurements of midbrain area and pons area, method of Oba [60]; **C.** coronalplane T1WI, atrophy of SCPs (arrows); **D.** concave margin of lateral margin of midbrain tegmentum — 'morning-glory' sign (arrows), deep and concave interpeduncular fossa (star)

higher indicates the possibility of PSP-RS [59, 61]. Recently, an MRPI of 2.0 incorporating the third ventricular width was introduced as an improvement on the initial index [59].

The MRPI and the P area/M area ratio have adequate diagnostic value to support the PSP-RS clinical diagnosis of PSP-RS, as opposed to PD and healthy controls, but they do not show anadequate sensitivity and specificity profile when differentiating PSP subtypes [54]. Midbrain area measurement is much easier for neuroradiologists to perform, has similar diagnostic potential to MRPI, and is significantly associated with greater ocular motor dysfunction at the time of MRI and more rapid disease progression at follow-up [62]. Callosal atrophy and mild cortical atrophy — usually restricted to the frontal lobes — are also observed [47].

The problem of MRI in PSP and MSA is the discrepancy between the red flags, and clinical symptoms and signs at the early stages, combined with the typical delay of the MRI and changes three or more years on from disease onset [63, 64]. Scans should therefore be repeated at the follow-up, but, by that time, the clinical picture usually shows the typical symptoms (severe dysautonomia, ataxia, falling and moderate/mild LD response in MSA; ophthalmoplegia with frequent falls and cognitive decline with frontal behaviour in PSP; unilateral [or mostly pronounced] apraxia, dystonia, myoclonus and alien limb phenomenon along with cognitive decline in corticobasal syndrome). Therefore, these distinctive neuroimaging features are not very helpful at the very early disease stages.

Functional imaging of dopaminergic system with DaTSCAN

DaTSCAN, is one of the methods used to assess the nigrostriatal dopaminergic system and, more specifically, the intactness of the presynaptic dopaminergic terminals. In idiopathic PD, binding of the Dopamine Transporter (DaT) is often first reduced in the putamen contralateral to the clinically predominant side. The reduction in tracer uptake then progresses to the contralateral putamen and anteriorly as well as ipsilaterally to the caudate as a result of a specific pattern of nigrostriatal neurons degeneration.

In atypical parkinsonism, both pre- and postsynaptic nigrostriatal synapses are involved. Uptake is already abnormal at

disease onset. Unfortunately, DaTSCAN does not distinguish between idiopathic PD and APS and, therefore, according to the MDS-2015 diagnostic criteria, it should not be used routinely [1, 65]. In uncertain cases, the examination can be complemented by assessing the postsynaptic part using specific ligands, e.g. IBZM [66, 67]. For example, postsynaptic striatal dopaminergic imaging is included in the PSP disease criteria as a supportive feature, along with predominant midbrain atrophy or hypometabolism [68].

[^{123}I] FP-CIT–DaTSCAN is approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a SPECT tracer for testing dopaminergic neuronal integrity in suspected parkinsonian syndromes. DaTSCANis registered in Europe and in the United States for differential diagnosis between neurodegenerative parkinsonism and ET (Level A). Additionally, DatSCAN is indicated for detecting the loss of nigrostriatal dopaminergic neuron terminals in patients with parkinsonian syndromes. This is especially relevant in the differential diagnosis between DLB and other dementias, particularly AD; in distinguishing between parkinsonism due to presynaptic degenerative dopamine deficiency and other forms of parkinsonism, e.g. between idiopathic PD and drug-induced (see clinicalvignette 2, Fig. 6), psychogenic or vascular parkinsonism; and in detecting the early phase of presynaptic parkinsonian syndromes [69]. Similarly, it can be useful to distinguish primary dystonia from PD with dystonia, especially with dystonia as a first manifestation of young onset PD [2] and dystonic tremor (labelled as SWEDDs) from PD [70]. The broad list of possible useful indications is summarised in Table 2. Importantly, DaTSCAN should always be interpreted together with structural studies (e.g. MRI). This improves the performance of functional imaging, and reduces the rate of misdiagnosed cases.

Table 2. Clinical indications for [^{123}I]-FP-CIT SPECT — DaTSCAN

1.	Early onset parkinsonism (especially with dystonia as a first symptom)
2.	Atypical tremor presentations difficult to distinguish between ET and parkinsonism
3.	Essential tremor plus
4.	Tardive (usually postneuroleptic) parkinsonism or tremor
5.	Toxic parkinsonism (manganese e.g. ephedron encephalopathy, carbon monoxide)
6.	Vascular and postanoxic parkinsonism
7.	Post-traumatic parkinsonism
8.	Dystonic tremor in young patients
9.	Functional parkinsonism (psychogenic)
10.	Functional tremor (psychogenic)
11.	Differentiating DLB from AD
12.	Isolates RBD
13.	Diagnostic accuracy in clinical trials

Clinical vignette 2

A 31-year-old female was diagnosed with schizoaffective disorder and aripiprazole was introduced. After five years, the patient experienced unilateral resting and kinetic tremor of the right arm. Neurodegeneration with iron accumulation and Wilson's Disease were excluded. The patient was diagnosed with tardive tremor. Aripiprazole was changed to olanzapine, lamotrigine and subsequently to quetiapine. Propranolol and anticholinergics (biperiden, pridinol) were ineffective. ten years after the disease onset, other minor parkinsonian symptoms occurred including asymmetric rigidity and bradykinesia. LD with benserazide 150 mg/day were administered. After three months, the patient required hospitalisation in the psychiatric department due to acute psychosis. At that time, all medications (LD and antipsychotics) were withdrawn (for an unknown reason) and she was treated with benzodiazepines. However, this resulted in severe exacerbation of the parkinsonian symptoms. On admission to the neurology department, severe parkinsonian symptoms with predominant bilateral resting, postural and kinetic tremor, generalised hypokinesia (inability to walk independently) and muscle rigidity were observed (Part III of Unified Parkinson's Disease Rating Scale score of 71 points (UPDRS). LD was re-introduced with a satisfactory effect on parkinsonism and without psychotic symptoms (UPDRS part III score of 34). She was discharged on 500 mg/d LD/benserazide, propranolol 30 mg/d, clozapine 100 mg/d and trazodone 75 mg/d. Due to the clinical uncertainty, DaTSCAN was later performed with abnormal results (Fig. 6) leading to the diagnosis of PD.

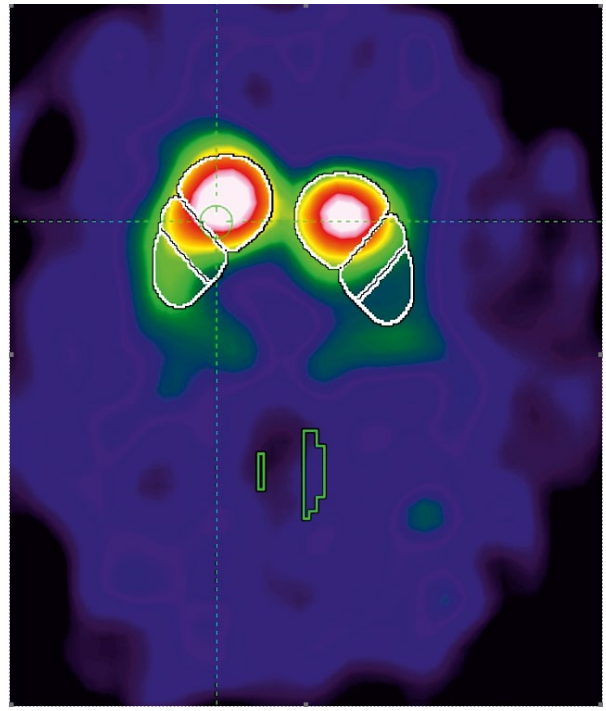

Figure 6. Clinical vignette 2 — abnormal [^{123}I]-FP-CIT SPECT (DaTSCAN) bilateral significant reduction of putamen DAT uptake

Table 3. Medication and drug abuse that may significantly influence visual and quantitative analysis of [^{123}I]-FP-CIT SPECT (modified from Darcourt et al. 2010) from Morbelli 2020 [69]

Drug class	Drug name	Effect on striatal [^{123}I] FP-CIT SPECT binding
Cocaine		May decrease (2 days)
Amphetamines	d-Amphetamine, methamphetamine, methylphenidate	May decrease (7 days)
CNS stimulants	Phentermine, ephedrines	May decrease, influences are likely when used as tablets (1 day)
Modafinil		May decrease (3 days)
Antidepressants	Mazindol, bupropion, radafaxine, sertraline	May decrease (3 days for mazindol, 8 days for bupropion)
Adrenergic agonists	Phenylpherine, norepinephrine	May decrease, influences are likely when infused as high doses
Anticholinergic drugs		Benztropine may decrease, other anticholinergicsmay increase this ratio, which will likely not affect visual assessments
Opioids	Fentanyl	May decrease (5 days)
Anesthetics	Ketamine, PCP, isoflurane	May decrease, of interest particularly for animal SPECT studies, although ketamine and PCP are sometimes used illicitly (1 day)

In brackets, time interval approximately equal to 5 half-times

This case shows the typical complications of neuroleptic therapy (tardive dyskinesia). Neuroleptic treatment was probably a trigger that revealed asymptomatic parkinsonism. A DaTSCAN performed earlier would have helped to avoid hospitalisation and potentially severe consequences.

DaTSCAN should definitely not be used at a patient's request, but rather the decision should be based on clinical judgement. It can also be useful in differentiating between AD and DLB [71]. In DLB, similar to idiopathic PD and APS, the DaTSCAN is abnormal, whereas in AD, the nigrostriatal pathway remains intact. Recent diagnostic recommendations for DLB suggest that a reduced DaT uptake in the basal ganglia, demonstrated by SPECT or PET (positron emission tomography), is an indicative biomarker. Supportive biomarkers include relative preservation of medial temporal lobe structures on a CT/MRI scan, generalised low uptake on a SPECT/PET perfusion/metabolism scan, and reduced occipital activity (the cingulate island sign) on [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging [72]. Additionally, newly described specific pattern found in DLB and Posterior Cortical Atrophy called the 'occipital tunnel' sign can be useful to distinguish this disease from AD. It is recommended, similarly to DaTSCAN, to use semiquantitative automated assessment to assist visual reading because this provides increased specificity and increased reading confidence, especially for less experienced readers [73].

The revised criteria for DLB clearly distinguish between clinical features and diagnostic biomarkers. Indicative biomarkers include reduced DaT uptake in the basal ganglia, demonstrated by SPECT or PET, together with a low uptake of [^{123}I]-mIBG (meta-iodobenzylguanidine) in myocardial scintigraphy imaging [72]. However, up to 10% of patients at the time of clinical diagnosis may show normal DaT uptake. In these patients, repeating the DaTSCAN should be considered [74]. [^{123}I]-mIBG is an analogue of noradrenaline, transported in the noradrenaline granule at sympathetic nerve terminals; it visualises cardiac sympathetic innervation and, in this way, reflects cardiac sympathetic integrity, which is preserved in AD and also in MSA. Reduced uptake is consistent with the loss of sympathetic terminals in the hearts in patients with DLB and PD.

It is recommended to avoid taking multiple medications that might significantly affect the visual and semiquantitative analysis of DaT-binding ligands, before DaTSCAN examination.

In this regard, patients should be withdrawn from (if possible) such medications for at least five half-lives period (supplementary material: Table 3). Single administration of iodide is recommended at least an hour before injection of the radiopharmaceutical to reduce ^{123}I exposure to the thyroid gland. Three to six hours are required for the agent to achieve appropriate concentration in the brain after the injection of the DaT ligand. Acquisition with the gamma camera takes about 30–45 minutes.

An array of software tools and methods are used to calculate semiquantification of the ratio activity in the putamen and caudate compared the activity in the reference region with the lowest number of DaT (occipital lobe).

Additionally, results are compared to data from the European Normal Control Database of DaTSCAN or the Parkinson Progression Markers Initiative, which provides age- and gender-specific reference values [75, 76]. This demonstrates that normal ageing is associated with about 5.5–6% signal loss per decade. PPMI additionally includes data from longitudinal assessment in PD patients showing that SBR (Specific Binding Ratio) is approximately 20 times higher compared to normal ageing.

In summary, the addition of quantification to visual analysis increases sensitivity, specificity and reader confidence [77].

SPECT/PET perfusion/metabolism imaging

Neuroimaging with DaTSCAN is limited in the differential diagnosis of APS and PD. In this regard, FDG-PET or [99mTc] HMPAO/ECD SPECT can be helpful due to disease-specific, characteristic patterns of hypometabolism [78] in FDG-PET. Currently, the role of FDG-PET in patients with neurodegenerative parkinsonian syndromes – especially with dementia – is recommend by experts in three clinical scenarios [73, 79]:

- for differentiating between PD and PSP with a typical posterior pattern of hypoperfusion of the midbrain, anterior cingulate, medial frontal cortex, striatum and thalamus (in PD — the striatum metabolism is preserved);
- for suggesting underlying pathophysiology in corticobasal degeneration, as FDG- PET scans could help to orient the investigation toward the underlying neuropathology (aetiological diagnosing) in corticobasal syndrome: the more posterior pattern (parietal and posterior cingulate) typical of CBS-AD; the anterior cingulate and caudate hypometabolism typical of CBS-PSP; and the hypometabolism of the basal ganglia and the lateralised hypometabolism in the cortex in CBS-CBD. A common pattern in CBD is characterised by asymmetric basal ganglia and cerebral cortical hypometabolism, mainly expressed in the frontoparietal area, contralateral to the clinically more affected side [80] (Fig. 7);
- for diagnosis of DLB, as FDG-PET enables differentiation between DLB (posterior pattern: lateral temporal, posterior parietal hypometabolism, prominent involvement of the lateral and mesial occipital hypometabolism [with marked hypometabolism of the praecuneus] with relatively preserved posterior cingulate metabolism — the so-called 'island' sign) and AD. This examination is mentioned as a supportive feature in the revised diagnostic criteria for this disease [72].

Differential diagnosis of PD and MSA-P still remains difficult in the early stages; cerebellar hypometabolism (although typically more for MSA-C) can be visible with FDG-PET, which seems to be superior to SPECT perfusion imaging [80].

In summary, despite the very limited high-quality evidence for the use of FDG-PET, the majority of the panellists shared the opinion that FDG-PET is a clinically useful imaging biomarker for idiopathic PD and atypical parkinsonism associated with dementia [79].

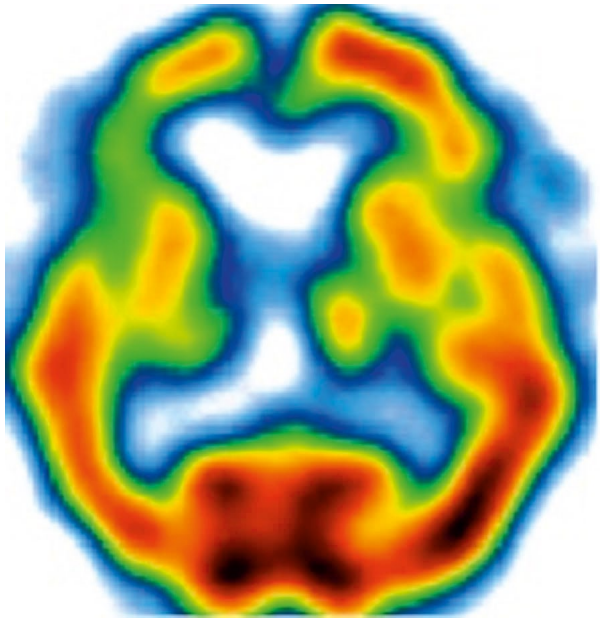

Figure 7. Corticobasal degeneration ([99mTc]-HMPAO SPECT) with asymmetric perfusion of basal ganglia and cerebral cortical hypoperfusion, mainly expressed in frontotemporal area, contralateral to clinically more affected side

Future directions

Research into the implementation of new MRI techniques that could prove useful in the diagnostics of idiopathic PD and APS is ongoing, but most of them as yet have only group-level diagnostic utility. The wider use of 3T MRI would be essential, especially for the assessment of nigrosome-1, as a potential marker of SN pathology [81]. However, for DNH evaluation there is a need for reproducible and standardised MR protocols including new techniques such as susceptibility map-weighted imaging (SMWI) or quantitative susceptibility mapping (QSM) [33].

Conclusions

MRI is a useful tool when the clinical picture suggests atypical or symptomatic parkinsonism, especially when LD response is limited. The key is to exclude treatable causes of parkinsonian symptoms, and therefore we recommend MRI scanning for all eligible patients. In future, with the increasing availability of 3T MRI scanners, establishing protocols for diagnosing nigrosome-1 could help to shape more precise diagnoses of PD and APS. DatSCAN should be performed in cases of uncertainty, but it should be avoided as a routine conformation of PD.

Hypometabolism of specific brain areas, with characteristic patterns for APS, may be detected by FDG-PET (SPECT perfusion is less sensitive) and helpful in diagnostic work-up, but it should be interpreted with caution and always within the spectrum of clinical examination. More research is needed to prove its utility in clinical practice.

Most importantly, patients should be primarily examined by specialists experienced in movement disorders, which should result in a significant reduction in the number of performed scans. As we mentioned, up to half of patients referred for this examination by GNs, and further re-examined by movement disorder specialists, did not need any scanning because their clinical histories and symptoms were sufficient to make a proper diagnosis [3].

A network of specialists in movement disorders is required, which would enable a better, faster and more precise diagnosis of parkinsonism. This would also minimise the costs of unnecessary tests and enable patients to be treated according to the most up-to-date standards [63].

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