Differentiating multiple system atrophy from Parkinson’s disease: contribution of striatal and midbrain MRI volumetry and multi-tracer PET imaging

M Ghaemi, R Hilker, J Rudolf, J Sobesky, W-D Heiss

Objectives: The differential diagnosis between typical idiopathic Parkinson’s disease (PD) and the striatonigral variant of multiple system atrophy (MSA-P) is often difficult because of the presence of signs and symptoms common to both forms of parkinsonism, particularly at symptom onset. This study investigated striatal and midbrain findings in MSA-P and PD patients in comparison with normal controls with the use of positron emission tomography (PET) and three dimensional magnetic resonance imaging (3D MRI) based volumetry to increase the differential diagnostic accuracy between both disease entities.

Methods: Nine patients with MSA-P, 24 patients with PD, and seven healthy controls were studied by MRI and PET with 6-[18F]-fluoro-L-dopa (FDOPA), [18F]fluoro-deoxyglucose (FDG), and 11-C-Raclopride (RACLO). Striatal and extrastriatal volumes of interest (VOI) were calculated on the basis of the individual MRI data. The PET data were transferred to the VOI datasets and subsequently analysed.

Results: MSA-P differed significantly from PD patients in terms of decreased putaminal volume, glucose metabolism, and postsynaptic D2 receptor density. The striatal FDOPA uptake was equally impaired in both conditions. Neither MRI volumetry nor PET imaging of the midbrain region further contributed to the differential diagnosis between PD and MSA-P.

Conclusions: The extent and spatial distribution of functional and morphological changes in the striatum permit the differentiation of MSA-P from PD. Both, multi-tracer PET and 3D MRI based volumetry, may be considered equivalent in the assessment of different striatal abnormality in both disease entities. In contrast, MRI and PET imaging of the midbrain does not provide a further gain in diagnostic accuracy.

The differential diagnosis between idiopathic Parkinson’s disease (PD) and parkinsonism predominant multiple system atrophy (MSA-P) is often difficult, particularly at symptom onset. To find the correct diagnosis early in the course of the disorders is, however, of major importance with respect to prognostic aspects and therapeutic strategies. In particular, MSA-P may present with signs and symptoms in early stages of the disease that are also common to PD. MSA-P was first identified by Adams and colleagues in four patients with severe, progressive parkinsonism in whom postmortem examination disclosed extensive loss of striatal neurons, particularly in the putamen, as well as degeneration of the substantia nigra, while Lewy bodies, the histopathological hallmark of idiopathic PD, were absent. Clinically, MSA-P is an akinetic-rigid syndrome characterised by gait disturbance, rigidity, progressive bradykinesia, and a poor response to dopaminergic therapy.

The identification of patients with clinically probable MSA-P is challenging in view of the lack of definite diagnostic tests to confirm the clinical suspicion of atypical parkinsonism. Neuropathological studies demonstrated that about 20% of patients clinically diagnosed as PD proved to have had another neurodegenerative disorder at postmortem examination and that signs and symptoms typical for the presence of PD (resting tremor, levodopa responsiveness) could also be found in necropsy verified MSA-P patients who were diagnosed in life as having PD.

In the past, functional brain imaging with positron emission tomography (PET) had been proved to be of some value for the differential diagnosis of parkinsonism. However, PET imaging was largely restricted to the measurement of striatal function. Because of the recent development of high resolution PET scanners and three dimensional magnetic resonance imaging (3D MRI) based methods of PET data analysis, extrastriatal cerebral regions can now also be investigated. In addition, 3D MRI volumetry has become available and has been recently applied in patients with PD, MSA-P, and progressive supranuclear palsy (PSP).

The aim of this study was to evaluate whether the combined measurement of striatal and midbrain regions of interest as well as the use of two independent imaging modalities with multi-tracer PET and 3D MRI volumetry might further increase the diagnostic power in the distinction between PD and MSA-P. We hypothesised that extrastriatal histopathological changes in MSA-P might find correlates in these imaging modalities and focused on the midbrain as the extrastriatal region of choice, as a more extensive cell loss in the substantia nigra and locus coeruleus had been described in patients with MSA than in PD.

METHODS

Study subjects

Twenty four patients with PD diagnosed according to the UK brain bank criteria (118 men and 6 women, mean (SD) age 53.0 (11.0) years; mean (SD) Hoehn and Yahr (HY) score 1.9 (1.1); mean (SD) Unified Parkinson’s Disease Rating Scale (UPDRS) total score 1.9 (1.1); mean (SD) Unified Parkinson’s Disease Rating Scale; PSP progressive supranuclear palsy.

Abbreviations: PET, positron emission tomography; MRI, magnetic resonance imaging; PD, Parkinson’s disease; MSA, multiple system atrophy; FDG, [18F]fluoro-deoxyglucose; RACLO, 11-C-Raclopride; VOI, volumes of interest; HY, Hoehn and Yahr score; UPDRS; Unified Parkinson’s Disease Rating Scale; PSP progressive supranuclear palsy.

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Subjects laid comfortably in supine position in a room with dimmed lighting and low background noise. The PET scans were performed using the ECAT EXACT® and ECAT EXACT HR positron scanner® (Siemens CTI, Knoxville, TN, USA) yielding 47 contiguous transaxial image planes (slice thickness of 3.375 mm or 3.125 mm, respectively, with a full width at half maximum axial resolution of 5.8 and 3.6 mm). We used a 3D data acquisition mode to increase the sensitivity of the brains’ signal to noise ratio, which obtains a higher spatial resolution and a reduction of the partial volume effect. Images were reconstructed on a 128×128 matrix with 2.17 mm pixel size.

FDG

Cerebral glucose metabolism was measured after injection of 370 MBq of FDG. Regional cerebral metabolic rates of glucose (rCMRGlc) were calculated using the autoradiographic model with a fixed lumped constant of 0.42 and the rate constant K, adjusted to measured tissue activity.20

RACLO

A bolus of 370 MBq of 11C-raclopride (specific activity 30–70 GBq/µmol) was injected. Scanning began after a 30 second background frame recording a total of six serial time frames with 10 minute duration over a 60 minute study period.

Data analysis

Each MRI scan was reoriented three dimensionally to the anterior to posterior commissural (AC-PC) line, and exact 3D alignment of the PET scans with the MRI was obtained using a previously described coregistration procedure.22 The dataset of the reoriented MRI scan was subjected to a subtle analysis tool that permits the exact three dimensional definition of even small structures.22 The following volumes of interest (VOIs) were manually defined by outlining the appropriate anatomical structures in transverse slices of the individual T1 weighted MRI on both hemispheres: caudate nucleus, putamen (separated in two parts: anterior and posterior part), and midbrain. The upper border of the midbrain VOI was defined on the plane showing the mammillary bodies and the optic nerves, respectively, and the lower pontine border on the level of the middle cerebellar peduncle. After interactive VOI definition, their overall volumes were calculated by adding the volumes of all segmented voxels. Subsequently, corresponding volumes of both hemispheres were averaged. The advantage of

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**Table 1** Characteristics of the parkinsonian study subjects

<table>
<thead>
<tr>
<th>Controls (n=7)</th>
<th>PD (n=24)</th>
<th>MSA-P (n=9)</th>
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<tr>
<td>Age</td>
<td>53.4 (11.9)</td>
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<td>Disease duration</td>
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<td>HY score</td>
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<td>1.9 (1.1)</td>
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<td>UPDRS total score</td>
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<td>35.3 (27.2)</td>
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PD, idiopathic Parkinson’s disease; MSA-P, striatonigral variant of multiple system atrophy. HY, Hoehn/Yahr Score; UPDRS, Unified Parkinson’s Disease Rating Scale. †p<0.0001 versus PD (ANOVA and post-hoc Scheffé test). Data shown as mean (SD).

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**Table 2** Clinical features of the nine study subjects with MSA-P

<table>
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<tr>
<th>Patient</th>
<th>Dysarthria</th>
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this type of data analysis is the exact definition of VOIs on the individual MRI scan for each patient as well as the formulation of MRI based volumetric data.

Using a fusion of individual PET images with the three-dimensional VOI set, result values for the three different PET datasets were calculated for each VOI. FDOPA influx constants (K_i), which represent the rate of striatal FDOPA uptake and storage, were calculated using a multiple time graphic analysis approach with an occipital instead of an arterial plasma function. Furthermore, we determined regional cerebral metabolic rates of glucose (rCMRGlc) for each VOI. To reduce intersubject variability, the rCMRGlc values were normalised by division with the global metabolic rate of glucose of the entire brain (gCMRGlc).

Specific RACLO binding indices of the striatal VOIs were calculated with the cerebellum as dopamine-receptor free reference region using the following ratio index: (target VOI activity – cerebellum activity)/cerebellum activity. To capture local differences in putaminal function, we calculated a percentage binding gradient between the anterior and posterior part of the putamen for each PET tracer defined as the difference between both parts of the nucleus in relation to the activity of the entire putamen, which was set as 100%. Negative values of the anterior-posterior gradient indicated more extensive decreases of the detected radioactivity within the posterior part of the putamen.

Statistical analyses were performed using SPSS for Windows 10.0 (SPSS UK Ltd, Surrey, England). Intergroup comparisons of metric data were performed with univariate analysis of variance (ANOVA) followed by Scheffé’s test for correction of multiple comparisons. The level of statistical significance was set at p<0.05.

RESULTS

Clinical data

The study subjects were well matched for age (table 1). Disease severity measured with the total UPDRS score was significantly higher in the MSA-P group (66.4 (15.4)) compared with PD subjects (35.3 (27.2)), whereas the disease duration was nearly identical in both patient groups (5.2 (4.7) years in PD versus 4.9 (2.7) years in MSA-P).

Striatal imaging

Compared with healthy controls, putaminal FDOPA K_i values were significantly reduced in the MSA-P as well as in the PD group (p<0.0001) (table 3). The decrease of FDOPA storage was mostly pronounced in the posterior putamen in both leading to a negative anterior-posterior gradient of radiotracer binding within this nucleus that was nearly identical in MSA-P (−46.8 (23.3)%) and in PD subjects (−49.8 (22.4)%). In both groups, the negative FDOPA gradient was significantly higher than in healthy controls (−3.2 (6.6)%, p<0.001) (fig 1).

At the postsynaptic dopamine receptor level, MSA-P patients showed a significant reduction of all putaminal RACLO binding indices versus controls (p<0.05) and versus PD (p<0.0001; table 3). The reduction of RACLO binding was most prominent in the posterior putamen, which resulted in a RACLO binding gradient of −19.8 (15.3) % and mimicked the intranuclear anterior-posterior gradient of the FDOPA influx constants. In contrast, an increased RACLO uptake within the entire putamen was found in the PD cohort that reached the highest level in the posterior part of the nucleus (positive RACLO binding gradient of +1.9 (9.2)%) and that was significantly higher compared with MSA-P subjects.

In MSA-P, the putaminal but not caudate rCMRGlc was significantly decreased compared with controls and PD patients (table 3). This finding was independent of the brains’ global metabolic rate of glucose, as nearly identical statistically significant results were obtained after normalisation of the rCMRGlc values (table 3).

In MSA-P patients, the volumes of all putaminal VOIs were significantly reduced to approximately 50% of those of controls and PD patients (table 3). No significant striatal differences between PD patients and healthy controls were found in FDG-PET and MRI volumetry.
We found a small trend towards lower midbrain FDOPA Ki
nucleus (fig 2C and D). Individual data in MRI-volumetry and the posterior part of
MSA-P from PD and controls with the least overlap of
disorders but not between MSA-P and controls (fig 2B).
Receptor status differed adequately between the parkinsonian
values were higher in PD than in controls, the dopamine
MSA-P subjects (fig 2A). As the putaminal RACLO binding
parkinsonian subjects in the putamen but not between PD and
PET, we found a good discrimination between controls and
between the study subgroups in either modality. In FDOPA-
caudate nucleus did not show a sufficient discrimination
the striatal PET and MR imaging modalities. In general, the
This study is the first to combine PET and 3D MRI based volu-
metric striatal and extrastriatal imaging in the same
parkinsonian patients in order to differentiate between PD
and MSA-P patients, which is often difficult on clinical
findings alone. Our data suggest that putaminal RACLO-PET
and FDG-PET as well as 3D MRI based putaminal volumetry
are equivalent in their efficacy to distinguish PD from MSA-P
patients, whereas functional and morphological imaging of
the midbrain region does not provide a further gain in
diagnostic accuracy.
In view of these shortcomings of standard MRI approaches,
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Our PET data are in good agreement with previous findings in MSA and PD patients that showed decreases of the putaminal glucose metabolism and the postsynaptic dopamine receptor density exclusively in MSA, but not in levodopa responsive idiopathic PD. Histological and autoradiographic studies have shown that the levodopa resistance of motor symptoms as one key feature of MSA patients is associated with neuronal loss, gliosis, and loss of postsynaptic D2-dopamine receptors, preferentially in the posterior putamen. In a recent study, the application of diffusion weighted MRI imaging (DWI) in parkinsonian subjects discriminated PD from MSA-P patients by showing increased putaminal diffusion coefficients solely in MSA-P. This finding most probably reflects ongoing degeneration in MSA-P patients and corresponds to our putaminal FDG-PET and RACLO-PET findings. In contrast, we were able to demonstrate that the presynaptic dopaminergic deficit measured with FDOPA-PET does not differentiate between PD and MSA-P, as striatal FDOPA influx constants are reduced to a comparable degree and show an intranuclear gradient with lower values in the posterior part of the putamen in both disease entities. This finding is in line with histopathological data that found the most pronounced dopaminergic cell loss in the posterior part of the putamen in MSA patients.

The overlap of individual striatal imaging data in our study subjects suggests that MSA-P is most reliably separated from PD by putaminal FDG-PET and MRI based volumetry data with the least overlap of values in the posterior part of the putamen. Therefore, the application of either imaging modality or their combination can be recommended for differential diagnostic purposes in case of atypical parkinsonism. While FDOPA-PET did not prove to be useful in the differentiation between MSA-P and PD, the putaminal RACLO binding also showed sufficient discrimination between slightly decreased tracer binding levels in MSA-P and remarkably increased binding levels in PD. However, other groups also reported decreased striatal RACLO binding in advanced PD patients with a fluctuating response to levodopa medication. Therefore, the discrimination ability of RACLO-PET might be restricted, as it seems to strongly depend on clinical characteristics of PD patients.

With the use of PET, a reduction of striatal glucose consumption and of dopamine D2 receptor binding was also shown in patients with sporadic and familiar progressive supranuclear palsy (PSP), another important differential diagnosis of atypical parkinsonism. In some patients, it is therefore difficult to decide whether the cause of atypical parkinsonism is MSA-P or PSP, even if striatal multi-tracer PET imaging is undertaken. To ensure reliability of our data, only patients with atypical parkinsonism fulfilling common diagnostic criteria of MSA-P and without cardinal features of PSP such as supranuclear vertical gaze palsy, predominant

Figure 2 Scatter plots showing individual striatal PET (A; FDOPA, B: RACLO, C: FDG) and MRI based volumetry data (D) of controls (open squares), PD (black circles), and MSA-P study subjects (grey triangles). Within the putamen, a sufficient discrimination between controls and parkinsonian subjects as well as a substantial overlap between PD and MSA-P is obvious in FDOPA-PET. Putaminal RACLO binding is higher in PD than in controls and differentiated between the parkinsonian disorders, but not between MSA-P and controls. Putaminal FDG-PET and MRI volumetry clearly separated MSA-P from PD and controls with the least overlap of individual data in MRI volumetry and the posterior part of the nucleus.
axial rigidity, and dementia. were included in the study. However, it has to be kept in mind that PET imaging or MRI volumetry is suitable to differentiate between PD and atypical parkinsonism, but has less diagnostic power to discriminate MSA-P from PSP, particularly in early disease stages in which a clinical differentiation is not yet obvious.

In the midbrain region, neither MRI volumetry nor PET imaging offered additional information for a better discrimination of PD and MSA-P. We did not expect this finding because, even though the distribution pattern of nigral degeneration may be similar in MSA-P and PD, neuronal loss has been shown to be more extensive in MSA than in PD in neuropathological studies. Further studies yielded evidence that the cell loss is not only related to the nigrostriatal, but also to the reticulotegmental projections. For example, 5-hydroxytryptamine (5-HT)1B receptors were examined with the use of [3H]sumatriptan as radioligand in posterior striatal and midbrain postmortem tissue sections of patients who died from various degenerative movement disorders. While no significant change in the density of [3H]sumatriptan binding sites was found in the striatum and substantia nigra in PD patients, [3H]sumatriptan labelling was almost absent in MSA-P. Moreover, degeneration of the pontine noradrenergic locus coeruleus that may be involved in autonomic function and sleep-wake cycle regulation had been described in MSA and PD.

Despite the occurrence of a more extensive and multi-transmitter affecting cell loss in MSA-P we were not able to discriminate the parkinsonian study subgroups from each other and from healthy controls by means of midbrain PET imaging. The reasons for this finding remain speculative, as our study provides the first data on midbrain FDOPA activity in probable MSA-P patients and just a few studies are available on extrastriatal changes of FDOPA uptake in PD.

In general, the cerebral FDOPA uptake mainly represents the intracellular enzymatic turnover of the radiotracer by the aromatic amino acid decarboxylase (AADC). A common AADC enzyme is responsible for the decarboxylation of both levodopa in catecholaminergic and 5-hydroxytryptophan in serotonergic neurons. FDOPA-PET is not specific for dopaminergic neurons, but measures the activity of monoaminergic neurons in general. The midbrain as defined in our study included one dorsally located area comprising the serotonergic raphe nuclei and mesopontine segments with close topographical relations to catecholaminergic (locus coeruleus) as well as dopaminergic neurons (substantia nigra, retrorubral nucleus, ventral tegmental area). In previous studies performing voxel-by-voxel based analysis of FDOPA PET data with statistical parametric mapping, Ito et al. found decreased K values bilaterally in the substantia nigra of PD patients, whereas Rakhi and coworkers demonstrated significant increases of midbrain FDOPA activity in early, but significant reduction of midbrain FDOPA K in advanced PD patients compared with controls. These apparently conflicting results indicate that the midbrain FDOPA PET signal presumably represents a complex summation of transmitter activity within monoaminergic neurons of the upper brainstem. It may be hypothesised that the PET signal reflects not only cell loss but also compensatory upregulation mechanisms in intact monaminergic neurons.

Similar to FDOPA, we failed to demonstrate significant differences in midbrain FDOP-5ET and in MRI volumetry in our study population. Presumably, MSA-P has its main pathological changes within the striatum and the substantia nigra, while infratentorial areas are more severely and earlier affected in MSA-C. De Volder et al. studied seven patients with probable MSA-P and found a significantly decreased glucose utilisation in the putamen, caudate nucleus, and frontal cortex but not in the thalamus or cerebellum. Asato and coworkers showed that 76% of MSA-C, but only 44% of MSA-P patients had a pontine diameter smaller than the lower limit of the normal range. Therefore, imaging of the midbrain region might be of discriminant value in MSA-C, but shows no significant changes in MSA-P. However, another FDG-PET study showed similar levels of hypometabolism in the striatum as well as the cerebral cortex, thalamus, brainstem, and cerebellum in MSA and sporadic OPCA patients. Schulz and coworkers found a significant reduction of mean brainstem MRI volumes in patients with MSA-P and MSA-C. However, with the exception of MSA-C, the individual brainstem volumes of MSA subjects showed an extensive overlap with the range of normal controls. Moreover, it has to be kept in mind that our data and the above cited MRI volumetric data are not directly comparable, as we focused our investigation on the rostral part of the brainstem, namely the midbrain region.

In conclusion, our data suggest that volumetric analysis of MRA data permits a clear distinction between PD and MSA-P and reports a considerable putaminal neuronal loss in MSA-P patients. The degeneration of striatal nuclei in MSA-P is also functionally reflected in a corresponding reduction of local glucose consumption estimated with FDG-PET and of postsynaptic dopamine-D2 receptor density measured with RACLO-PET. However, striatal FDOPA influx constants as a measure of intact presynaptic dopaminergic nerve terminals, as well as MRI volumetry and PET imaging of the extrastriatal midbrain region, do not permit a distinction between the two disease entities. Our results indicate that both putaminal PET and MRI based volumetry may be considered equivalent in the differential diagnosis between PD and MSA-P. The alternative use of any diagnostic procedure can be recommended depending on its individual local availability.

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Differentiating multiple system atrophy from Parkinson’s disease