No relevant midbrain atrophy in Parkinson's disease

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ABSTRACT

Aims of the study To investigate whether significant midbrain atrophy is present in Parkinson's disease (PD), and if so, whether it can be used as a marker of striatal dopaminergic degeneration.

Methods In total, 150 PD patients and 155 controls were scanned with both brain dopamine transporter (DAT) [123I]FP-CIT SPECT and 1.5T MRI. Midbrain atrophy was measured from sagittal MRIs using the midbrain-to-pons ratios. Both striatal region-of-interest-based (Brass) and striatal and extrastriatal voxel-by-voxel-based DAT binding (SPM8) were investigated in relation to midbrain atrophy.

Results The midbrain-to-pons ratios in PD patients were slightly lower than those in the controls (mean 0.59 vs 0.61, $P < 0.05$). The ratios did not significantly correlate with striatal or extrastriatal [123I]FP-CIT uptake in controls or patients with PD.

Conclusions Mild midbrain atrophy is present in PD and can be detected with MRI. However, the midbrain atrophy in PD is not associated with the level of striatal dopaminergic dysfunction, and midbrain measurements therefore cannot be used as a clinically useful predictor of dopamine function.

INTRODUCTION

Midbrain atrophy is a well-known MRI-detected sign in patients with progressive supranuclear palsy (PSP). It is reflected in the hummingbird sign, which appears to show some specificity for PSP (1, 2), although negative results have also been reported (3). Midbrain atrophy can also be observed in vascular parkinsonism (4), primary progressive apraxia of speech (5), and dementia with Lewy bodies (6). The Parkinson plus phenotype with early falls and supranuclear vertical gaze palsy seems to be particularly associated with midbrain atrophy (7). Previous studies with small samples have suggested that Parkinson's disease (PD) is not associated with significant midbrain atrophy (1, 2).

In the only previous imaging study on this topic, Arnold et al. (8) investigated midbrain atrophy and striatal dopamine D2 receptor binding in 13 patients with possible or probable PSP. They concluded that midbrain atrophy correlated with a reduction in striatal D2 receptor binding, and that striatal damage and midbrain atrophy occur in parallel in PSP. If a strong correlation between striatal dopamine function and midbrain volume also occurs in non-PSP patients, simple midbrain measurements from conventional brain MRIs could be used to estimate the level of nigrostriatal dopamine function. In that case, MRI measurements of the midbrain could replace dopamine transporter (DAT) SPECT imaging in the differential diagnosis of PD.

We therefore aimed to investigate first whether midbrain atrophy is present in PD and can be detected with conventional brain MRI, and second, whether there is a clinically

relevant positive correlation between midbrain size and striatal dopamine function. A correlation between midbrain atrophy and DAT binding in both PD and PSP would indicate a clinically useful biomarker for dopaminergic degeneration. A large sample of patients with PD and subjects with normal brain dopamine function were included to maximize study power and minimize the risk of false negatives.

METHODS

Study subjects

In total, 150 PD patients and 155 controls were scanned with [123I]FP-CIT SPECT for clinical purposes as previously described (9). The PD patients had abnormal SPECT scans with a clinical diagnosis of idiopathic PD, and the controls were symptomatic subjects (mostly with mild bradykinesia, tremor, rigidity or gait/balance problems) with normal SPECT scans and no evidence of PD or other dopaminergic degenerative parkinsonism syndrome.

The classification (normal/ abnormal) was based on the initial clinical (visual with or without semiquantitative) judgment of a nuclear medicine physician. According to the Finnish clinical practice guidelines, United Kingdom PD Society Brain Bank Criteria (10) were used for diagnosing PD. Specific striatal binding ratios (SBRs) of [123I]FP-CIT uptake were generated automatically using Brass (Hermes Medical Solutions, Stockholm, Sweden) as described (9).

In addition, corresponding wholebrain regional SBRs were analyzed voxel by voxel using Statistical Parametric Mapping software (SPM8, Wellcome Trust Center for Neuroimaging, London, UK, www.fil.ion.ucl.ac.uk/spm/ software/spm8/), as described previously (11). The included subjects also underwent a conventional brain 1.5T MRI, with a mean interval of 6.5 (SD 8.3) months between SPECT and MRI scans.

This study was approved by the ethical committee of the local hospital district and was conducted according to the principles of the Declaration of Helsinki.

Measurement of the midbrain-to-pons ratios

Sagittal conventional T1 or T2 MRI images were used for the measurement of the midbrain-topons ratios using a simplified version (2) of the methodology described by Massey et al. (1). A midline sagittal level was used, and three line measurements over the pons (non-atrophied reference region) and the midbrain were drawn (the measurements were perpendicular to the visually estimated oblique superior–inferior axes) by one of the investigators (J. I.) blinded to diagnoses. The three measurements were averaged, and the mean values were used to calculate the midbrainto- pons ratios (the midbrain width divided by the pons width) (2).

Statistical analyses

Pearson partial correlation coefficients between SBRs and the midbrain-to-pons ratios were calculated using age, sex, scanner, scanning interval between SPECT and MRI, symptom duration, symptom type (tremor/no tremor), predominant side of symptoms, and medication as covariates. PD patients and controls were compared with ANCOVA using the same covariates as in the correlation analyses. P-values <0.05 were considered statistically significant. In the corresponding SPM analyses, cluster- or voxel-level family-wise error corrected P-values <0.05 within the entire search volume (all brain regions showing specific [123I]FP-CIT binding) were considered significant.

RESULTS

The demographic and clinical data are presented in Table 1. Patients with PD had 43.9% lower mean striatal [123I]FP-CIT uptake ($P < 0.0001$) and 3.3% lower midbrain-to-pons ratios ($P < 0.05$) compared to the controls (Table 1). There were 18 PD patients with abnormal midbrain-to-pons ratios (ratio < 0.52) and 132 PD patients with normal midbrain-to-pons ratios (ratio > 0.52). There were no differences in striatal DAT binding between patients with normal and abnormal midbrain- to-pons ratios [the mean (95% CI) striatal SBRs in patients with abnormal and normal midbrain- to pons ratios: 1.44 (1.17–1.72) and 1.47 (1.26–1.68), respectively, $P = 0.83$].

The midbrain-to-pons ratios did not significantly correlate with striatal FP-CIT uptake in the controls ($r = 0.02–0.13$, $P > 0.10$; Fig. 1A), in patients with PD ($r = –0.04$ to 0.00, $P > 0.65$; Fig. 1B), or in patients with abnormal midbrain-to-pons ratios in combination with abnormal SPECT ($r = –0.47$ to $–0.08$, $P > 0.16$). Voxel-based SPM analysis of [123I]FP-CIT uptake did not show any striatal or extrastriatal regions that correlated with midbrain-to-pons ratios in the whole sample or in PD patients and controls separately ($P > 0.05$).

DISCUSSION

The results indicate that, although there may be slight midbrain atrophy in PD, there is no relationship between midbrain atrophy and striatal dopamine function in PD or in subjects with normal dopamine function. Therefore, midbrain atrophy measurements cannot be used to estimate the level of presynaptic dopaminergic activity. An earlier study by Arnold et al. (8) demonstrated a moderate correlation between striatal dopamine receptor binding and midbrain atrophy in 13 patients with clinically possible and probable PSP. Their study did not include PD patients or controls, whereas our study did not include patients with PSP. Thus, the connection between midbrain atrophy and striatal dopamine function may be specific for PSP pathology. PSP is a progressive tauopathy with pathological findings including neuronal loss, gliosis and protein tau inclusions in neurons and glial cells, primarily in the basal ganglia, brainstem, and cerebellum (12). It may be that the tau burden of the midbrain, not the specific loss of dopaminergic neurons, is associated with midbrain atrophy. Clinicopathological studies have suggested that midbrain atrophy detected with MRI is histologically consistent with atrophy of the periaqueductal gray matter, quadrigeminal plate, and tegmentum (13). More importantly, the severity of atrophy appears to be closely related to the density of tau-positive structures such as neurofibrillary tangles, glial fibrillary tangles, and neuropil threads (13). We propose that even though midbrain atrophy and striatal dopaminergic defects may coexist, particularly in patients with PSP, the findings are not directly related but mirror separate mechanisms of the disease. Our results suggest that there may be slight midbrain atrophy also in patients with PD. We are not aware of any previous large-scale studies that have compared midbrain atrophy in patients with PD to that in controls with normal dopaminergic function. Because the diagnoses in the present

study were clinical, it is, however, possible that some PD patients were misdiagnosed patients with early PSP. Even if this is the case, the correlations between midbrain atrophy and DAT binding were clearly negative. Therefore, midbrain MRI cannot be used as a predictor of dopamine function, and it does not play a clinically relevant role in the differential diagnosis of PD. Because our PD patients were all at early stages of the disease, we cannot exclude a link between midbrain atrophy and DAT in advanced PD. However, a correlation in advanced PD would not have much influence on the diagnostic process. In addition, one must bear in mind that PD is associated with a spectrum of motor and non-motor symptoms with both dopaminergic and non-dopaminergic mechanisms (14–16). It is therefore possible that different motor (17) and non-motor subtypes (18) have distinctive effects on midbrain and striatal DAT binding. To conclude, we did not find meaningful correlations between midbrain atrophy and striatal DAT binding in patients with PD. Although PD appears to be associated with slight midbrain atrophy, it is not a marker of striatal dopaminergic dysfunction.

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Conflict of interests

Authors declare no conflict of interest.

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Table 1. The main demographic and clinical characteristics of the studied sample. The means (SD) are presented for continuous variables. [^{123}I]FP-CIT specific binding ratios (SBRs) and the MRI measurements are covariate-adjusted means from the ANOVA model with 95% confidence intervals.

	Parkinson's disease	Controls	*P*-value
n	150	155	-
Age (yrs)	64.9 (10.6)	62.1 (11.7)	0.16[a]
Sex (m/f)	91/59	78/77	0.08[b]
Interval between MRI and SPECT (months)	6.5 (8.3)	6.4 (9.5)	0.97[a]
SPECT scanner (I/II/III) [e]	54/60/36	60/57/36	0.84[b]
Symptom duration at SPECT (yrs)	2.0 (2.3)	4.2 (7.3)	<0.0001[a]
Symptom type (no tremor/ tremor)	51/99	64/91	0.20[b]
Predominant side of motor symptoms (right/left/symmetric)	70/63/17	66/46/43	<0.001[b]
Medication (D/AD/none)[d]	30/5/115	20/26/109	<0.001[b]
Mean striatal SBR of [^{123}I]FP-CIT uptake	1.51 (1.40-1.62)	2.69 (2.60-2.79)	<0.0001[c]
Midbrain-to-pons ratio	0.59 (0.58-0.60)	0.61 (0.59-0.62)	0.04[c]
Pons width (mm)	17.4 (17.1-17.8)	17.1 (16.9-17.4)	0.10[c]
Midbrain width (mm)	10.3 (10.0-10.5)	10.4 (10.2-10.5)	0.57[c]

[a] Independent samples t-test
[b] Fischer's exact test or Chi-Square test
[c] One-way ANOVA with age, sex, interval, scanner, symptom duration, symptom type, predominant side and medication as covariates.
[d] Dopaminergic/antidopaminergic (neuroleptics)/none.
[e] Scanner I: Picker Irix gamma camera with ¾-inch crystals, Scanners II and III: GE Infinia II Hawkeye SPECT/CT with 3/8-inch crystals.

Figure 1. Midbrain-to-pons ratios plotted against the mean striatal [^{123}I]FP-CIT uptake in the controls (A) and patients with Parkinson's disease (B). All correlations were non-significant, including separate analyses of striatal subregions.