Apparent diffusion coefficient measurements of the middle cerebellar peduncle differentiate the Parkinson variant of MSA from Parkinson’s disease and progressive supranuclear palsy

Giuseppe Nicoletti,1 Raffaele Lodi,2,3 Francesca Condino,1 Caterina Tonon,2,3 Francesco Fera,1 Emil Malucelli,2 David Manners,2 Mario Zappia,4,7 Letterio Morgante,5 Paolo Barone,6 Bruno Barbiroli2,3 and Aldo Quattrone1

1Institute of Neurological Sciences, National Research Council, Mangone (Cosenza), 2Dipartimento di Medicina Clinica e Biotecnologia Applicata D. Campanacci, Universita’ di Bologna, 3Dipartimento dell’Area Radiologica, Policlinico S. Orsola, Bologna, 4Institute of Neurology, University Magna Graecia, Catanzaro, 5Department of Neuroscience, Psychiatry and Anesthesiology, University of Messina, Policlinico Universitario and 6Department of Neurological Sciences, University Federico II, Naples, Italy

7Present address: Clinica Neurologica I, Dipartimento di Neuroscienze, Università di Catania, Catania, Italy

Correspondence to: Raffaele Lodi, MD, Dipartimento di Medicina Clinica e Biotecnologia Applicata “D. Campanacci”, “Universita’ di Bologna, Policlinico S. Orsola, Via Massarenti 9, 40138 Bologna, Italy
E-mail: raffaele.lodi@unibo.it

Clinical differentiation of parkinsonian syndromes such as the Parkinson variant of multiple system atrophy (MSA-P) and progressive supranuclear palsy (PSP) from Parkinson’s disease is difficult in the early stage of the disease. In order to identify objective markers for differential diagnosis, we studied these three groups of patients with diffusion-weighted MRI (DWI). Sixteen MSA-P patients, 16 with PSP, 16 with Parkinson’s disease and 15 healthy volunteers were studied. Regional apparent diffusion coefficients (rADC) were determined in different brain regions including basal ganglia, thalamus, white matter, pons and middle cerebellar peduncles (MCPs). rADC calculated in the MCP completely differentiated MSA-P patients (median: 0.93 × 10^{-3} mm²/s) from PSP patients (median: 0.82 × 10^{-3} mm²/s, P < 0.001), Parkinson’s disease patients (median: 0.79 × 10^{-3} mm²/s, P < 0.001) and healthy volunteers (median: 0.81 × 10^{-3} mm²/s, P < 0.001). Other regions considered showed an overlapping among groups. DWI discriminates MSA-P from PSP and Parkinson’s disease and healthy volunteers on the basis of MCP rADC values. These in vivo results confirm the pathological findings that the majority of MSA-P patients have moderate or severe degenerative changes not only in the nigrostriatal but also in the olivopontocerebellar systems. Our findings indicate that, in order to substantially contribute to the in vivo differential diagnosis of MSA-P, PSP and Parkinson’s disease, rADC measurements should not be limited to the basal ganglia but should also include the MCP.

Keywords: diffusion imaging; middle cerebellar peduncle; multiple system atrophy; progressive supranuclear palsy; Parkinson’s disease

Abbreviations: ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; EPI = echo planar imaging; MCP = middle cerebellar peduncle; MSA = multiple system atrophy; PPV = positive predictive values; PSP = progressive supranuclear palsy; rADC = regional ADC; ROI = region of interest


Introduction
The clinical differential diagnosis between Parkinson’s disease, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) is difficult in the early stages of the diseases. Parkinsonian symptoms and signs may be a
prominent feature of both MSA (Quinn et al., 1989) and PSP. On the basis of symptoms at onset, MSA has been divided into two forms: MSA-C characterized by a predominance of cerebellar symptoms and MSA-P where parkinsonism is prevalent (Wenning et al., 1994; Gilman et al., 1998). An akinetic rigid Parkinson-like syndrome, often associated with postural instability, is reported in >90% of PSP patients (Nath et al., 2003).

Parkinson’s disease and MSA are both alpha-synucleinopathies (Spillantini et al., 1998; Wakabayashi et al., 1998). Pathologically, in Parkinson’s disease a massive loss of dopaminergic neurons in the pars compacta of the substantia nigra and intraneuronal Lewy bodies (intracellular inclusions of aggregated alpha-synuclein) are present (Fearnley et al., 1991). In MSA, neuronal loss and gliosis occur in the inferior olives, pons, transverse pontocerebellar fibres, cerebellum, substantia nigra, locus caeruleus, striatum and the intermediolateral column of the spinal cord (Wenning et al., 1996). In MSA-P, the nigrostriatal system is the main site of pathology but less severe degeneration can be widespread and usually includes the olivopontocerebellar system (Kume et al., 1993; Wenning et al., 1996). In MSA-C, mainly the olivopontocerebellar system is involved along with loss of pontine neurons and transverse pontocerebellar fibres and atrophy of middle cerebellar peduncles (MCPs) (Kume et al., 1993; Wenning et al., 1996). Unlike Parkinson’s disease and MSA, PSP is a tauopathy characterized, pathologically, by neuronal loss, granulovacuolar degeneration, gliosis and neurofibrillary tangles in the midbrain, pons and basal ganglia (Hauw et al., 1994).

Given the difficulties of a clinical diagnosis, conventional MRI has been extensively used to identify diagnostic markers for Parkinson’s disease, MSA and PSP. Brain MRI in Parkinson’s disease is generally normal, although subtle mesencephalic changes, of uncertain diagnostic value, have been reported (Schrag et al., 2000). In PSP, atrophy of the midbrain, third ventricle dilation and periaqueductal T2-hypointensities are present (Schrag et al., 2000; Warmuth-Metz et al., 2001); moreover, a reduction of the anteroposterior diameter of the midbrain on axial T2-weighted magnetic resonance images differentiates PSP from Parkinson’s disease (Bhattacharya et al., 2002). MRI may help distinguish the two forms of MSA: MSA-P shows putaminal atrophy, T2-hypointensity and ‘slit-like’ marginal hyperintensity of the putamen while MSA-C shows a pontine cruciform hyperintensity (‘hot-cross bun’ sign) on T2-weighted and proton density images (Savoiardo et al., 1990; Schrag et al., 2000; Yekhlef et al., 2000, 2003; Bhattacharya et al., 2002). MR spectroscopy studies have only been focused on differentiating between Parkinson’s disease and MSA (Davie et al., 1995; Barbiroli et al., 1999) or between Parkinson’s disease and atypical parkinsonian disorders (Federico et al., 1997).

Diffusion-weighted MRI (DWI) has been applied to the differential diagnosis of parkinsonian syndromes. DWI allows the assessment of the water apparent diffusion coefficient (ADC), a measure of tissue water diffusivity. ADC depends on the interactions between water molecules and the chemical environment as well as the structural barriers at cellular and sub-cellular level hindering their motion in vivo (Le Bihan et al., 1992). Typically, pathological processes that modify tissue integrity, like in neurodegenerative disorders, result in an increased ADC (Le Bihan et al., 1992). ADC values in the putamen of MSA-P have been shown to completely distinguish between MSA-P and Parkinson’s disease patients who demonstrated respectively high and normal putaminal ADC (Schocke et al., 2002). However, the same group showed that high ADC in the putamen, caudate and pallidus distinguishes PSP patients from Parkinson’s disease but not from MSA-P (Seppi et al., 2003).

In the present study, in order to identify objective diagnostic markers for differential diagnosis, we used DWI to extensively assess the ADC values in the brainstem, MCPs, basal ganglia and cerebral white matter regions in patients with Parkinson’s disease, MSA-P and PSP.

Patients and methods

Patients

Sixteen consecutive patients with Parkinson’s disease, 16 consecutive patients with MSA-P, 16 patients with PSP and 15 age-matched healthy controls were studied. Clinical diagnosis of Parkinson’s disease (Calne et al., 1992), MSA (Gilman et al., 1999) and PSP (Litvan et al., 1996) was made by a movement disorder specialist (G.N.) according to the established consensus criteria. All patients were evaluated clinically, tested for levodopa response, Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and examined with MRI. The levodopa response was considered good when the clinical improvement was ≥30%, and moderate when the clinical improvement was ≥20%; response was considered negative when a clinical improvement was not present. Cognitive functions were assessed with the MMSE (Folstein et al., 1975): a patient was categorized as demented when he/she had a score below the cut-off value compared with normative data corrected for gender, age and education (Crum et al., 1993). None of the controls had a history of neurological or psychiatric diseases. Informed consent was obtained from all participants.

Magnetic resonance imaging

MRI was performed using a 1.5 T GE Signa Horizon NV/i system equipped with a birdcage head radio-frequency coil for signal reception and an EchoSpeed gradient system providing a maximum gradient strength of 30 mT/m and maximum slew rate of 150 mT/m/ms. As previously reported (Lodi et al., 2004), structural and DWI images were obtained from the same 18–24 axial slices with 5-mm thickness and 1-mm inter-slice gap. T1-weighted structural imaging was performed with a spin-echo (SE) sequence with a flip angle α of 90°, a repetition time (TR) of 500 ms, an echo time (TE) of 10 ms, an isotropic spatial in-plane resolution of 0.94 mm and two signal averages. DWI (Le Bihan et al., 1986) was conducted using an SE single-shot echo planar imaging (EPI) technique (Mansfield et al., 1977) with a pair of Stejskal–Tanner diffusion weighting gradient pulses (Stejskal et al., 1965). The EPI sequence
was performed with $\alpha = 90^\circ$, TR = 10 s, TE = 100 ms, an in-plane resolution of 2.5 mm and phase encoding in anterior–posterior direction. The diffusion weighting gradients were applied on each of the three physical axes $x$, $y$, and $z$ in separate scans. Three different gradient strengths were chosen corresponding to $b$-factor values of 300, 600 and 900 s/mm$^2$. In addition, images without diffusion weighting were acquired corresponding to $b = 0$ s/mm$^2$ and exhibiting a T2-contrast.

An expert neuroradiologist (F.F.) blinded to the patient’s diagnosis qualitatively evaluated all the MR images. Conventional brain axial T1-weighted and proton density MR imaging scans were visually inspected for the presence or absence of putaminal atrophy, putaminal hypointensity, slit-like hypointensity in the posterolateral margin of the putamen, brainstem atrophy, hyperintensity of the MCPs and cruciform hyperintensity of the pons (‘hot-cross bun’ sign). Cruciform hyperintensity was considered as present if it was unequivocal on T2-weighted and proton density images.

**Data processing and evaluation**

In general, DW EPI images suffer from distortions due to eddy currents generated by the large gradients applied for diffusion weighting (Haselgrove et al., 1996). In this study, distortions were corrected by slice-wise registration of the DW images onto the T2-weighted EPI images using the image registration software FLIRT (www.fmrib.ox.ac.uk/flirt). Owing to the nature of the distortions, the degrees of freedom were restricted to translation, scaling, and shearing along the phase encoding direction, as also reported by Haselgrove et al. (1996).

Assuming a signal attenuation depending mono-exponentially on the $b$-value, the ADC of each direction was determined pixel-wise using a least-squares fit. By calculating the mean of the three directions, the ADC trace map was generated.

As previously reported (Lodi et al., 2004), in order to avoid contamination of the ADC values for grey and white matter by the much higher values of CSF during further evaluation, CSF was removed from the ADC map. This was accomplished using the FAST algorithm (www.fmrib.ox.ac.uk/flirt) for a two-class segmentation based on the corresponding T2-weighted EPI images. Finally, using FLIRT the diffusion data were registered onto the T1 scan and a region of interest (ROI) was then selected. ADC maps do not show clearly brain structures for the presence of intrinsic low contrast differences. Therefore, the ROIs were initially selected on the T1-weighted images, then checked on the T2-weighted EPI images—which has the same distortions from field inhomogeneities as the diffusion images—and finally transferred to the ADC maps for determination of the mean values in each ROI. Figure 1 illustrates the brain areas defined for regional ADC (rADC) calculation: left and right caudate, putamen, pallidus and thalamus, prefrontal and precentral white matter and MCPs. We selected ROIs of appropriate dimensions to minimize partial volume effects. In the basal ganglia and thalamus rADC were also calculated by including in the ROIs the whole individual brain structure. The spatial resolution of standard DWI images does not allow a reliable measurement of ADC values in the cerebral cortex and other brain structure like superior cerebellar peduncles (SCP) as partial volume effects cannot be avoided. Therefore, in the present study cortical or SCP ROIs were not selected. To evaluate the intrarater reliability, a second evaluation was made by the neuroradiologist (F.F.) who scored all the scans blindly.

**Statistical analysis**

The difference in sex distribution between MSA, PSP, Parkinson’s disease and controls was evaluated with $\chi^2$-test. One-way analysis of variance (ANOVA) followed by post hoc Bonferroni correction was performed for comparison of the age at examination, disease duration and age at onset. To assess the differences in Hoehn and Yahr ‘off’ stages and Unified Parkinson’s Disease Rating Scale (UPDRS) ‘off’ scores among patient groups a Kruskal–Wallis test was used, followed by a Mann–Whitney $U$-test for multiple comparisons where a significant difference was found. Resulting $P$-values were corrected according to Bonferroni. These tests were also used to evaluate the differences in MRI measurements among groups. To verify the agreement between left and right measures and to assess the intrarater reliability, the intraclass correlation coefficient was calculated. As a correlation measure between demographic and clinical variables, the Spearman coefficient was calculated. Sensitivity, specificity and positive predictive values (PPV) for differentiating MSA from PSP and MSA from Parkinson’s disease were calculated using the optimal cut-off values determined by ROC (receiver operating characteristic) curve analysis (Armitage et al., 2002). Optimal cut-off level was considered the value that has the highest sum of sensitivity and specificity.

Statistical analysis was performed with Statistical Package for Social Science Software (version 12.0, SPSS, Chicago, IL) for Windows.

**Results**

**Patients**

Table 1 shows demographic and clinical data of MSA-P, PSP, Parkinson’s disease patients and controls. There was a difference ($P = 0.007$) in sex distribution among groups: PSP versus MSA, and PSP versus healthy controls. However, in healthy controls there was no significant difference between rADC values of males and females in any brain area ($P > 0.05$). Thus the sex ratio bias should not affect rADC comparison. All Parkinson’s disease patients had a good levodopa response whereas only 1 out of 16 MSA-P patients had a moderate levodopa response and none of the PSP patients had a response to levodopa. None of the MSA-P patients presented ataxia or other cerebellar signs at the onset of the disease. However, after 3 years of disease two MSA-P patients developed ataxia that was evident at the moment of scan. No Parkinson’s disease patients were demented, whereas two MSA-P and three PSP patients showed dementia. The small number of patients with dementia does not allow the statistical correlation of this clinical feature with MRI and DWI findings. Structural MRI revealed a number of abnormalities in both MSA-P and PSP patients. Hyperintense putaminal rim was present in eight MSA-P patients, MCP hyperintensity in three and cruciform hyperintensity in four patients (two of whom with MCP hyperintensity). Midbrain atrophy was present in four MSA-P and eight PSP patients. Atrophy of the putamen was present in six MSA-P and eight PSP patients, putaminal hypointensity in five MSA-P and five PSP patients and pontine atrophy in six MSA-P and three PSP patients. More than one MRI abnormality was present in the
same MSA-P or PSP patient. MRI abnormalities were absent in Parkinson’s disease patients with the exception of putaminal hypointensity in two cases and midbrain atrophy in three.

**DWI**

Tables 2 and 3, and Fig. 2 show rADC values of the different brain regions selected in the three patient groups. The intraclass correlation coefficients showed a high agreement between left and right side \( (P < 0.001) \): putamen \((r = 0.710)\), caudate \((r = 0.700)\), globus pallidus \((r = 0.698)\), thalamus \((r = 0.721)\), prefrontal white matter \((r = 0.769)\), precentral white matter \((r = 0.846)\) and MCP \((r = 0.871)\). The intrarater reliability showed a high agreement between the first and the second measurement \( (P < 0.001) \) of the left side \((r \text{ range} = 0.86–0.91)\) and right side \((r \text{ range} = 0.84–0.94)\). Therefore,

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**Table 1** Demographic and clinical data of patients with MSA-P, PSP, Parkinson’s disease and controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex (M/F)*</th>
<th>Age (years), mean (SD)‡</th>
<th>Disease duration (years), mean (SD)†</th>
<th>Onset, mean (SD)‡</th>
<th>H–Y median* (range)</th>
<th>UPDRS median* (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA-P (16)</td>
<td>4/12</td>
<td>64.7 (5.1)</td>
<td>4.9 (4.0)</td>
<td>58.8 (6.5)</td>
<td>3.5 (3–5)</td>
<td>42.2 (29–80)</td>
</tr>
<tr>
<td>PSP (16)</td>
<td>13/3</td>
<td>70.7 (7.8)</td>
<td>3.3 (2.5)</td>
<td>67.3 (8.9)</td>
<td>4 (3–5)</td>
<td>48 (3–90.5)</td>
</tr>
<tr>
<td>Parkinson’s disease (16)</td>
<td>9/7</td>
<td>61.0 (7.7)</td>
<td>7.5 (5.8)</td>
<td>53.5 (8.6)</td>
<td>2.25 (1–3)</td>
<td>23.5 (12–40)</td>
</tr>
<tr>
<td>Controls (15)</td>
<td>5/10</td>
<td>67.3 (6.0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

H–Y = Hoehn–Yahr; UPDRS = Unified Parkinson’s Disease Rating Scale; *\(P = 0.007\) (\(\chi^2\)-test); †\(P = 0.029\) (one-way ANOVA); ‡\(P < 0.001\) (one-way ANOVA); *\(P < 0.001\) (Kruskal–Wallis test).
ADC values are reported as mean values. ADC values in the putamen, caudate, globus pallidus, thalamus, prefrontal and precentral white matter, MCP and pons, were significantly different among groups (Kruskal–Wallis test: \(P < 0.001\)). Post hoc testing with the Mann–Whitney U-test revealed an increase in putaminal ADC values in MSA-P patients compared with Parkinson’s disease patients (\(P < 0.001\)), controls (\(P < 0.001\) and PSP patients (\(P = 0.001\)); PSP patients revealed increased putaminal ADC values when compared with both Parkinson’s disease patients (\(P < 0.001\)) and controls (\(P = 0.001\)). Patients with MSA-P showed increased ADCs in the caudate nucleus compared with Parkinson’s disease patients (\(P = 0.016\) and controls (\(P < 0.001\)). Basal ganglia and thalamus ADC were also calculated by including the whole structure in the ROIs. The mean and individual results of each group of subjects matched those obtained by using geometrical ROIs (data not shown). As regards the MCP, MSA-P patients showed increased ADC values when compared with Parkinson’s disease (\(P < 0.001\)), PSP patients (\(P < 0.001\)) and controls (\(P < 0.001\)). Basal ganglia and thalamus ADC were also calculated by including the whole structure in the ROIs. The mean and individual results of each group of subjects matched those obtained by using geometrical ROIs (data not shown). As regards the MCP, MSA-P patients showed increased ADC values when compared with Parkinson’s disease (\(P < 0.001\)), PSP patients (\(P < 0.001\)) and controls (\(P < 0.001\)); PSP patients did not show increased ADC values when compared with Parkinson’s disease patients and controls. Moreover, none of the MCP ADC values in the MSA-P group surpassed the highest value in the Parkinson’s disease, PSP and control groups. This lack of overlap was also present for each value of the left and right MCP ADC in the MSA-P patients versus Parkinson’s disease and PSP patients and in both of the two mean MCP measurements performed. The increase in ADC values in MCP of MSA-P patients did not correlate with the presence of increased signal intensity: the three MSA-P patients with MCP hyperintensity showed mean ADC values (0.90, 0.92 and 0.93 \(\times 10^{-3}\) mm²/s) within the range of MCP ADC values found in patients without MCP hyperintensity (0.90–1.17 \(\times 10^{-3}\) mm²/s, range). Table 3 also shows the results for the other brain regions. When we considered the ROC curve analysis, only MCP ADC values differentiated MSA-P group (median: 0.93 \(\times 10^{-3}\) mm²/s; range: 0.89–1.17 \(\times 10^{-3}\) mm²/s) from both PSP (median: 0.82 \(\times 10^{-3}\) mm²/s; range: 0.71–0.85 \(\times 10^{-3}\) mm²/s) and Parkinson’s disease groups (median: 0.79 \(\times 10^{-3}\) mm²/s; range: 0.73–0.85 \(\times 10^{-3}\) mm²/s) with a sensitivity of 100%, a specificity of 100% and a PPV of 100% (Table 4). Sensitivity is the proportion of MSA-P patients with ADC values > 0.875 (MSA-P versus PSP) and >0.87 (MSA-P versus Parkinson’s disease); specificity is the proportion of Parkinson’s disease or PSP patients with ADC values < 0.875 (MSA-P versus PSP) and <0.87 (MSA-P versus Parkinson’s disease); and PPV is the probability of a person with an ADC value > 0.875 (MSA-P versus PSP) or >0.87 (MSA-P versus Parkinson’s disease) to have MSA-P. When comparing putaminal ADC values in PSP and Parkinson’s disease patients, with a cut-off \(\geq 0.93\), sensitivity was 75%, specificity 100% and PPV 100%.
Finally, as regards the MCP, there was a correlation between rADC and age at examination \((P = 0.021)\) only for Parkinson’s disease patients. There were no correlations between MCP rADC values and other clinical variables considered (age at onset, disease duration, Hoehn–Yahr, UPDRS) in MSA, PSP or Parkinson’s disease patients.

### Discussion

Over the last few years a number of MRI studies have been focused on the identification of diagnostic markers helpful in the differential diagnosis of parkinsonian syndromes such as MSA, PSP and Parkinson’s disease. In the present DWI study we show that ADC values are increased in the MCP of MSA-P patients and that ADC measurement of MCP can distinguish PSP and Parkinson’s disease from MSA-P patients with 100% sensitivity and 100% specificity.

Studies performed using conventional MRI (Schrag et al., 2000), quantitative volumetric MRI (Paviour et al., 2005) and DWI (Schocke et al., 2002; Seppi et al., 2003) have identified a number of imaging abnormalities that can distinguish with high sensitivity and specificity patients with atypical parkinsonian syndromes (MSA-P and PSP) from Parkinson’s disease patients who in general have normal scans.

On conventional MRI (axial T2-weighted and proton density), typical abnormalities for MSA-P include hyperintense putaminal rim, putaminal hyperintensity and atrophy of the dentate nucleus, while MSA-C patients may show a signal increase in the cerebellum, MCPs, and a cruciform hyperintensity in the pons (‘hot-cross bun’ sign) (Savoiardo et al., 1990; Schrag et al., 2000; Yekhlef et al., 2000, 2003; Bhattacharya et al., 2002). In PSP patients common MRI abnormalities comprise a reduction of the anteroposterior midbrain diameter < 14 mm (Warmuth-Metz et al., 2001), signal increase in the midbrain, atrophy or signal increase of the red nucleus, frontal or temporal lobe atrophy (Schrag et al., 2000). It has recently been reported that the evaluation of the midbrain area on mid-sagittal MRI can differentiate PSP from Parkinson’s disease and MSA-P, but not MSA-P from Parkinson’s disease (Oba et al., 2005). Despite the identification of MRI changes specific for MSA and PSP, the neuroimaging differentiation of patients with atypical parkinsonism is still challenging. As also shown in our groups of parkinsonian patients, MR findings often misclassify patients already with a clinical diagnosis of PSP or MSA (Schrag et al., 2000), and both conventional imaging (Schrag et al., 2000) and DWI (Seppi et al., 2003) may show overlapping abnormalities in MSA and PSP patients. rADC values and diffusion tensor trace values [Trace(D)] have been found to be increased in the putamen of MSA-P patients (Schocke et al., 2002, 2004) and in the putamen, caudate and pallidus of PSP patients (Seppi et al., 2003) compared with Parkinson’s disease patients. rADC and Trace(D) of the putamen could discriminate well between MSA-P and Parkinson’s disease patients (Schocke et al., 2002, 2004) but putamen rADC values showed an almost complete overlap when MSA-P and PSP patients were compared (Seppi et al., 2003).

In our series of patients as in the study of Seppi et al. (2003) putaminal rADC values discriminate MSA-P from Parkinson’s disease patients with 100% sensitivity, specificity and PPV whereas putaminal rADC showed a slightly lower sensitivity (75% compared with 90%) in association with the same specificity and PPV (= 100%) in discriminating PSP from Parkinson’s disease patients. Both MSA and PSP are characterized pathologically by a selective neuronal loss and gliosis predominantly affecting the basal ganglia (Hauw et al., 1994; Wenning et al., 1997), and this pathological process modifies tissue integrity, resulting in an increased ADC. We found high rADC values in the thalamus of PSP and MSA-P patients—this result confirming the presence of pathology in these conditions not only in the basal ganglia but also in the diencephalons (Dickson, 1999).

None of the putaminal rADC values in the Parkinson’s disease group was greater than the lowest value in the MSA-P group, and only four PSP patients showed putaminal rADC values within the Parkinson’s disease group range. Consistent with a previous study (Ohshita et al., 2000), we found increased rADC values in the prefrontal and precentral white matter of PSP compared with healthy controls. High rADC values may be the consequence of underlying pathological changes that may include the presence of fibrillary tangles in oligodendroglial cells in the white matter and axonal damage secondary to the deposition of neurofibrillary tangles in the cerebral cortex, especially the frontal and the precentral...
cortex. In our study, the assessment of prefrontal and precentral white matter rADCs in MSA-P and Parkinson’s disease patients revealed increased rADC in both groups of patients compared with healthy controls and did not allow us to discriminate MSA-P from PSP and Parkinson’s disease. The finding of increased rADC values in the frontal white matter in Parkinson’s disease patients extends the evidence that neurodegenerative changes may occur outside

differential diagnosis of MSA-P from Parkinson’s disease and PSP

Brain (2006), 129, 2679–2687 2685

Fig. 2 Scatterplot of MCP (A), caudate (B), pallidal (C) and putaminal (D) rADC values from MSA-P, PSP, PD patients and controls. It may be noted that only for MCP all rADC values in the MSA-P group were higher than the highest value obtained in the PD, PSP or controls.

Table 4 DWI differentiates MSA-P from PSP, Parkinson’s disease and controls

<table>
<thead>
<tr>
<th>Validity measures</th>
<th>MCP rADC</th>
<th>Putamen</th>
<th>Caudate</th>
<th>Pallidus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (MSA-P versus PSP)</td>
<td>$\geq 0.875 \times 10^{-3}$ mm²/s (%)</td>
<td>100</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Specificity (MSA-P versus PSP)</td>
<td>100</td>
<td>81.2</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>PPV (MSA-P versus PSP)</td>
<td>100</td>
<td>84.2</td>
<td>66.7</td>
<td>100</td>
</tr>
<tr>
<td>Sensitivity (MSA-P versus Parkinson’s disease)</td>
<td>$\geq 0.87 \times 10^{-3}$ mm²/s (%)</td>
<td>100</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Specificity (MSA-P versus Parkinson’s disease)</td>
<td>100</td>
<td>100</td>
<td>93.7</td>
<td>93.7</td>
</tr>
<tr>
<td>PPV (MSA-P versus Parkinson’s disease)</td>
<td>100</td>
<td>100</td>
<td>92.3</td>
<td>90.9</td>
</tr>
</tbody>
</table>
the substantia nigra in Parkinson’s disease. Significant increases in annual brain volume loss was found in nondemented Parkinson’s disease patients compared with control subjects (Hu et al., 2001). Consistently, frontal lobe atrophy correlated with duration of motor symptoms has been described as a feature of late-onset Parkinson’s disease (Double et al., 1996), and frontal lobe changes were found in Parkinson’s disease patients with early cognitive impairment and those with dementia (Owen et al., 1999).

In contrast with the findings in the basal ganglia where rADC values showed a large overlap in MSA-P, Parkinson’s disease and PSP patients groups, we found that in the MCP all rADC values assessed in the MSA-P patients were higher than the highest rADC values detected in PSP and Parkinson’s disease patients as well as in healthy controls (Table 2 and Fig. 2). High rADC values in the MCP of MSA-C patients in comparison with healthy controls have also been reported by a recent DWI study (Kanazawa et al., 2004). Although all Parkinson’s disease patients had rADC values within the normal range, as a group rADC correlated with age. There is no straightforward explanation for this finding that needs to be confirmed in a larger patient sample.

These in vivo results confirm the pathological findings that the majority of MSA-P patients have moderate or severe degenerative changes in the nigrostriatal and olivoponto-cerebellar systems (Wenning et al., 1997). Pontocerebellar fibres originate from pontine grey neurons, which possess axons that cross through the other side of the basilar pons, enter the MCP and terminate in the contralateral cerebellar cortex. The involvement of transverse myelinated pontocerebellar fibres can be seen on routine MRI as a pontine cruciform hyperintensity (the ‘hot-cross bun’ sign), a finding typically observed in MSA-C and in other pathological conditions selectively involving the pontocerebellar system (Savoiardo et al., 1990; Murata et al., 1998; Schrag et al., 1998).

In conclusion, we found a significantly increased rADC value in the MCP of MSA-P patients that allowed a complete discrimination of MSA-P from the other parkinsonian syndromes considered. The patient population we considered in this study is more affected than the population reported in other studies. However, this does not weaken the conclusions of our study. The PSP patients, who presented normal MCP rADC values, were more severely affected than MSA-P patients with high MCP rADC values and, in turn, showed a complete overlap of MCP rADC with Parkinson’s disease patients who were the least clinically affected. Our findings indicate that, in order to substantially contribute to the in vivo differential diagnosis between MSA-P, PSP and Parkinson’s disease, rADC measurements should not be limited to the basal ganglia but should also include the MCP. Our work further strengthens the view that DWI scan and rADC brain measurements should be included in the clinical work-up to differentiate between distinct parkinsonian disorders in vivo.

References


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