Diffusion-weighted brain imaging study of patients with clinical diagnosis of corticobasal degeneration, progressive supranuclear palsy and Parkinson’s disease

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Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are two neurodegenerative disorders within the category of tauopathies, which must be considered in differential diagnosis of Parkinson's disease. Although specific clinical and neuroradiological features help to guide the clinician to a likely diagnosis of Parkinson's disease, CBD or PSP, differential diagnosis remains difficult. The aim of our study was to analyse apparent diffusion coefficient (ADCave) maps from patients with clinical diagnosis of CBD (corticobasal syndrome, CBS), classical phenotype of PSP (Richardson's syndrome, RS) and Parkinson's disease (PD) in order to identify objective markers to discriminate between these groups. Thirteen Parkinson's disease patients, 10 RS patients, 7 CBS patients and 9 healthy volunteers were recruited and studied in a 1.5 T MR scanner. Axial diffusion-weighted images were obtained and the ADCave map was generated. Regions of interest (ROIs) included mesencephalon, corpus callosum and left and right superior cerebellar peduncle (SCP), thalamus, caudate, putamen, pallidus, posterior limb of internal capsule, frontal and parietal white matter. Histograms of ADCave were generated for all voxels in left and right cerebral hemispheres and in left and right deep grey matter regions separately, and the 50th percentile values (medians) were determined. The ratio of the smaller to the larger median value (symmetry ratio) was calculated for left and right hemispheres and for left and right deep grey matter regions (1 = perfect symmetry). Putaminal ADCave values in CBS and RS were significantly greater than those in Parkinson's disease patients, but could not distinguish CBS from RS patients. In CBS patients, the values of the medians of cerebral hemispheres histograms were significantly higher than those in RS, Parkinson's disease and healthy volunteers, while the hemispheric symmetry ratio in CBS (0.968, range 0.952–0.976) was markedly reduced compared with RS (0.993, range 0.992–0.994), Parkinson's disease (0.991, range 0.988–0.993) and healthy controls (0.990, range 0.988–0.993). The hemispheric symmetry ratio differentiated CBS patients from RS and Parkinson's disease patients with a sensitivity and specificity of 100%. In RS patients, the ADCave values of the SCPs were significantly greater than those in Parkinson's disease and healthy volunteers. Our findings confirm that putaminal ADCave values evaluation provides a good discrimination between Parkinson's disease and atypical parkinsonisms, including RS and CBS. Furthermore, diffusion-weighted imaging, by detecting the brain microstructural correlates of the typical asymmetric signs and symptoms in CBS and the SCP involvement in RS, was shown to aid characterization and differentiation of atypical parkinsonism.

Keywords: diffusion imaging; corticobasal degeneration; progressive supranuclear palsy; Richardson's syndrome; Parkinson's disease

Abbreviations: CBD = corticobasal degeneration; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy; DWI = diffusion-weighted imaging; ADC = apparent diffusion coefficients; ROI = region of interest; SCP = superior cerebellar peduncle; PPV = positive predictive values; NPV = negative predictive values


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Introduction

Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are sporadic neurodegenerative disorders characterised by multisystem degeneration and tau pathology of both neuronal and glial cells (Hauw et al., 1994; Dickson et al., 2002). In CBD signs and symptoms are related to basal ganglia dysfunction (asymmetric parkinsonism, rigidity, gait disturbances) and cortical dysfunction (apraxia, alien-limb phenomenon, dementia) (Lang et al., 1994; Kumar et al., 1998). Clinical features related to the dysfunction of basal ganglia are also present in PSP patients (akinetic-rigid syndrome) but in general are symmetric and associated with the impairment of infratentorial structures (vertical gaze palsy, early falls) (Litvan et al., 1996). Notwithstanding such differences in clinical presentation, there remains an overlap in symptoms between CBD and PSP making the differential diagnosis between these neurodegenerative disorders challenging (Boeve et al., 2003; Scaravilli et al., 2005). Moreover, in the early stages of disease, it may be difficult to differentiate CBD and PSP from Parkinson’s disease (Lang et al., 1994; Kumar et al., 1998).

Conventional and advanced quantitative MR techniques are used extensively to improve the diagnostic accuracy of different forms of parkinsonism (Hauser et al., 1996; Barbiroli et al., 1999; Soliveri et al., 1999; Schrag et al., 2000; Yekhlef et al., 2003; Righini et al., 2004; Seppi and Schocke, 2005; Arai, 2006; Groschel et al., 2006). Conventional MR is in general normal in Parkinson’s disease patients (Seppi and Schocke, 2005), whereas atrophy and signal changes of specific brain areas have been reported in both PSP and CBD, mostly in subjects with only a clinical diagnosis. In PSP patients, atrophy of the midbrain and the superior cerebellar peduncle (SCP), dilatation of the third ventricle and T2-periaqueductal hyperintensities are often present (Schrag et al., 2000; Yekhlef et al., 2003; Righini et al., 2004; Seppi and Schocke, 2005; Arai, 2006; Groschel et al., 2006). Fewer MRI studies have been conducted in pathologically (Schrag et al., 2000) or clinically diagnosed CBD (Hauser et al., 1996; Soliveri et al., 1999) patients. These have reported cortical atrophy, frequently asymmetric and mainly frontoparietal, putaminal hypointensity and increased signal intensity in the motor cortex and subcortical white matter on T2-weighted images. Nevertheless, the diagnostic accuracy of MRI abnormalities is suboptimal for clinically diagnosed PSP (sensitivity averaging around 70% across different studies) (Schrag et al., 2000; Yekhlef et al., 2003; Righini et al., 2004; Groschel et al., 2006) and poor for CBD (Schrag et al., 2000; Josephs et al., 2004).

Diffusion weighted imaging (DWI) is able to identify spatially resolved micro-structural brain damage, via the apparent diffusion coefficient (ADC), which is typically elevated in brain areas where neurodegeneration occurs. This has led to an increasing use of DWI in the diagnostic investigation of neurodegenerative parkinsonian syndromes such as Parkinson’s disease, PSP and MSA (MSA-P) (Schocke et al., 2002, 2004; Blain et al., 2006; Nicoletti et al., 2006; Seppi et al., 2003, 2006a, b; Nilsson et al., 2007; Paviour et al., 2007). Several studies have shown that DWI/DTI investigations may help in differentiating PSP and MSA-P from Parkinson’s disease patients on the basis of increased basal ganglia ADC or diffusion trace values (Schocke et al., 2002, 2004; Nicoletti et al., 2006; Seppi et al., 2003, 2006a, b). Increased diffusivity has been found in atypical parkinsonism compared with Parkinson’s disease patients and controls mostly in the putamen and, in some but not all studies, also in the caudate nucleus, globus pallidus and thalamus (Schocke et al., 2004; Nicoletti et al., 2006; Seppi et al., 2003, 2006b). It has been shown that putaminal ADC can separate MSA-P from Parkinson’s disease patients with high sensitivity (ranging from 93% to 100% in different studies) and specificity (100%) and PSP from Parkinson’s disease patients (sensitivity: 75–90%; specificity: 100%), but is unable to distinguish between PSP and MSA-P patients (Seppi et al., 2003; Nicoletti et al., 2006). It may be possible to differentiate between PSP and MSA-P by considering the ADC of additional brain structures specifically affected, such as the middle cerebellar peduncles, where ADC is higher in MSA-P patients compared with PSP patients (sensitivity 91–100%, specificity 84–100%) (Blain et al., 2006; Nicoletti et al., 2006; Nilsson et al., 2007; Paviour et al., 2007), or in the mesencephalon (at the level of the decussation of the SCP), where ADC values are increased in PSP patients compared with Parkinson’s disease and MSA patients (Blain et al., 2006; Nilsson et al., 2007). To date, no DWI/DTI studies have been performed in CBD patients.

A definite diagnosis of neurodegenerative parkinsonisms can be made only by post-mortem examination. CBD is characterized by the presence of neurofilament-positive ballooned neurons and tau-positive ballooned bodies, threads and astrocytic plaques, affecting cardinal structures particularly in the cerebral cortex, basal ganglia and thalamus (Dickson et al., 2002), while PSP is diagnosed if there are tau-positive globose neurofibrillary tangles, coiled bodies, threads and tufted astrocytes affecting cardinal nuclei particularly in the basal ganglia, subthalamus and brainstem (Dickson et al., 2007). In a recent clinicopathologic analysis of a large series of patients, it was shown that the clinical diagnosis of PSP is confirmed pathologically in most cases, but the clinical diagnosis of CBD was confirmed pathologically only in 50% of cases (Josephs et al., 2006b). It has been shown that some patients with a clinical diagnosis of CBD are affected not only by corticobasal degeneration but also by other tauopathies, such as Pick disease and PSP, or by Alzheimer diseases or prion diseases (Josephs et al., 2004, 2006b). The evidence of this poor clinico-pathological correlation has led to the use of the term corticobasal syndrome (CBS) in the case of a clinical diagnosis of CBD.

The clinico-pathological correlation is much stronger for PSP although a clinical presentation of PSP may also
sometimes be associated with pathological features of CBD, Lewy body disease, multiple system atrophy or Alzheimer disease (Josephs et al., 2003; Mizuno et al., 2005). Some authors have recently returned to use the term Richardson’s syndrome (RS) referring to the classic clinical phenotype of PSP (Williams et al., 2005).

In the present study, we used DWI to identify objective markers to discriminate patients with a clinical diagnosis of CBD—reported here as CBS—from patients with the classic clinical phenotype of PSP—reported here as RS—and Parkinson’s disease. ADC maps were analysed by region of interest (ROI) as well as by the calculation of median ADC values for each hemisphere.

Methods
Subjects
We studied 13 patients with a clinical diagnosis of Parkinson’s disease, 10 with a clinical diagnosis of classic phenotype of PSP (RS), 7 with a clinical diagnosis of CBD (CBS) and 9 healthy volunteers (Table 1). Patients were consecutively recruited from the Movement Disorders Center of the Department of Neurological Sciences between September 2005 and September 2006. Diagnoses were made according to the Brain Bank criteria for Parkinson’s disease (Gibb and Lees, 1988; Hughes et al., 1992), the Litvan criteria for PSP (Litvan et al., 1996) and the Lang and Kumar criteria for CBD (Lang et al., 1994; Kumar et al., 1998). In particular, a diagnosis of RS was made if the extrapyramidal features were symmetric and if there was any combination of early falls, supranuclear gaze palsy, axial more than appendicular rigidity, akinnesia and levodopa unresponsiveness. A diagnosis of CBS required the presence of slowly progressive asymmetric akinetic-rigid syndrome not responsive to levodopa therapy, the presence of unilateral ideomotor apraxia, sensory deficit of cortical origin or alien limb syndrome and unilateral myoclonus or dystonia. Clinical symptoms and stages were quantified using the motor examination part of Unified Parkinson’s Disease Rating Scale (UPDRS-III) (Fahn and Elton, 1987) and the Hoehn and Yahr (H&Y) staging (Hoehn and Yahr, 1967). A clinical follow-up was conducted regularly until August 2007, and in that period, none of the patients had changed diagnostic category. None of the control subjects had MRI abnormalities or a history of neurologic or psychiatric diseases. Informed consent was obtained from each patient and normal volunteer.

MRI imaging protocol
Subjects were studied in a 1.5 T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner. Structural imaging included sagittal and axial T1-weighted spin-echo scans and axial T2-weighted fast spin-echo scans.

As previously reported (Lodi et al., 2004), axial DW images were obtained (slice thickness = 5 mm, inter-slice gap = 1 mm) using a single-shot EPI sequence (matrix size = 192 x 192 mm²). Orthogonal x, y and z diffusion-encoding gradients were applied with gradient strengths corresponding to b-values of 300, 600 and 900 s/mm². In addition, images without diffusion weighting were acquired, corresponding to b = 0 s/mm² and exhibiting T₂-contrast. The total DWI scan time was 2 min.

Data analysis
In general, DW EPI images suffer from distortions due to eddy currents generated by the large gradients applied for diffusion weighting. In this study, distortions were corrected by slice-wise registration of each EPI image onto the first T2-weighted EPI image using the image registration software FLIRT (www.fmrib.ox.ac.uk/flirt). The ADC in each direction was then determined pixel-wise using a least-squares fit, assuming a signal attenuation depending mono-exponentially on b-value. The ADC average (ADCave) map was generated by calculating the mean of three orthogonal directions.

Two raters (GR and RL), one (RL) with >10 years neuroimaging experience, qualitatively evaluated all the MR images, while blinded to the subjects’ diagnosis. The two raters separately assessed MR images for the presence of atrophy and signal changes. Sagittal and axial T1-weighted spin-echo images were evaluated in particular for the presence of atrophy of cerebral cortex, corpus callosum, putamen, midbrain and SCP, and dilation of the third ventricle; axial T2-weighted fast spin-echo scans were inspected for the presence of signal intensity changes (in particular, putaminal hypointensity and midbrain and white matter hyperintensities). In case of disagreement between the raters on any of the parameters reported above, the images were reevaluated by both until a consensus was reached (Righini et al., 2004).

ROIs were defined to include corpus callosum (genu and splenium), mesencephalon (decussation of the SCP, DSCP and left and right SCP, thalamus, caudate, putamen, pallidus, posterior limb of internal capsule and frontal and parietal white matter. Working on axial images we were not able to select the middle part of the corpus callosum. Figure 1 shows some of the selected ROIs. Basal ganglia, thalamus and the posterior limb of the internal capsule were delineated separately as whole structures in at least two consecutive slices. Also the SCPs were delineated as a whole structure, but given their small dimensions, in a single slice. The ROIs of the genu and splenium of the corpus callosum were delineated in the most representative axial image. Geometrical (square) ROIs were used to calculate ADCave values in the

Table I  Demographic and clinical data of subjects studied

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Sex (M/F)</th>
<th>Age (years), mean ± SD</th>
<th>Onset (years),a mean ± SD</th>
<th>Disease duration (years),b mean ± SD</th>
<th>UPDRS-III, median (range)</th>
<th>H &amp; Y stage, median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBS (7)</td>
<td>0/7</td>
<td>71 ± 8</td>
<td>67 ± 10</td>
<td>4 ± 3</td>
<td>23 (12–52)</td>
<td>2.5 (2–4)</td>
</tr>
<tr>
<td>RS (10)</td>
<td>6/4</td>
<td>62 ± 7</td>
<td>57 ± 6</td>
<td>4 ± 3</td>
<td>26 (18–48)</td>
<td>2.5 (2–4)</td>
</tr>
<tr>
<td>Parkinson’s disease (13)</td>
<td>7/6</td>
<td>62 ± 10</td>
<td>48 ± 8</td>
<td>14 ± 8</td>
<td>26 (6–49)</td>
<td>2.5 (1.5–3)</td>
</tr>
<tr>
<td>Controls (9)</td>
<td>7/2</td>
<td>63 ± 4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*aFor indicated variables one-way ANOVA showed inter-group differences: P < 0.01."
mesecephalon at the decussation of SCP and in the frontal and parietal white matter. Cerebral cortical ROIs were not selected, because substantial partial volume effects from subcortical white matter and CSF could not be avoided. For a global evaluation of brain ADCave values, histograms of ADCave were generated for all pixels in left and right cerebral hemispheres separately, including cortical areas in the analysis (Fig. 2A and B) (Martinelli et al., 2007). To minimise partial volume effects due to CSF, for both cortical and peri-ventricular brain structures a threshold for ADCave values was used (see below). Furthermore, histograms of ADCave were generated for all pixels in left and right deep grey matter separately (selected area included putamen, caudate, pallidus and thalamus). To exclude voxels containing only CSF from the ADCave histograms, we adopted a threshold value of 2.4 × 10^{-3} \text{mm}^2/\text{s} following previous published work (Martinelli et al., 2007). The non-Gaussian ADCave distribution was assessed by finding the 50th percentile values (medians) along with the mean. We calculated the ratio of the smaller 50th percentile value (numerator) to the greater (denominator) within left and right hemispheres and within left and right deep grey matter regions. We termed the results the hemispheric symmetry ratio and deep grey matter symmetry ratio (1 = perfect symmetry). Using the same method, the symmetry ratio was also calculated for each ROI.

The evaluation of DWI data was performed by two raters (CT and GR), one (CT) with 7 years neuroimaging experience, each blinded to the subjects’ diagnoses.

**Statistical analysis**

Statistical analyses were performed using SPSS 14.0 for Windows. One-way analysis of variance (ANOVA) followed by a post hoc Dunn–Sidack correction (Sokal and Rohlf, 1995) was performed for comparison of the age at examination, age at onset and disease duration. The statistical comparison of H&Y stages, UPDRS ‘off’ scores and ADCave values between all the groups was performed using non-parametric tests, as sample sizes were small and Kolmogorov–Smirnov testing showed that most of the variables were not normally distributed. The Kruskall–Wallis test was used to test whether significant intergroup differences occurred, with a statistical significance taken as $P<0.05$. Where such differences were found, multiple-group comparisons were performed using a post hoc Mann–Whitney U-test. In order to limit Type I errors due to the multiple group comparisons, a more stringent significance threshold was adopted, of $P<0.0085$, according to Dunn–Sidack method [$\alpha_T = 1 - (1-\alpha)^{1/k}$].

Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for differentiating the groups were calculated using the optimal cut-off values determined by receiver operating characteristic (ROC) curve analysis. The cut-off level giving the highest sum of sensitivity and specificity was considered to be optimal. For correlations between DWI and clinical parameters, we used the Spearman rank test with a statistical significance taken as $P<0.05$. Inter-rater reliability was assessed using the Bland–Altman method (Bland and Altman, 1986); the mean difference, SD of the differences and 95% limits of agreement (i.e. mean difference ± 2SD) were calculated for each parameter.

**Results**

**Patients**

Demographic and clinical data of patients studied are reported in Table 1. Patients’ ages were not significantly different between groups. A significant difference was found for age at onset and disease duration: Parkinson’s disease patients had a younger age at onset ($P<0.01$) and a longer disease duration ($P<0.01$) compared with either RS or CBS patients. The age at disease onset was greater in CBS than in RS patients, but it just failed to reach statistical significance ($P = 0.06$), while the disease duration was similar in both groups. There were no differences in UPDRS off scores or in Hoehn and Yahr stages for any of the patient groups.
All patients fulfilled diagnostic criteria at the time of MRI scan and at the end of follow-up.

Structural MRI revealed a mildly asymmetric cortical atrophy in 2/4 RS patients with fronto-parietal atrophy. Cortical atrophy was present in all CBS patients, clearly asymmetric in two and mildly asymmetric in two patients. The following structures were atrophic: corpus callosum (three CBS, one RS patient), midbrain (one CBS, five RS), SCPs (one CBS, five RS), putamen (CBS, four RS). Mesencephalic tegmental hyperintensity was detected only...
in three RS patients, putaminal hypointensity in four RS and two CBS patient. The only MRI abnormalities detected in Parkinson’s disease patients were a mild cortical frontal atrophy in four cases and putaminal hypointensity in three cases. All healthy subjects showed normal MRI scans.

**DW imaging**

**ROI analysis**

Right- and left-side ADCave values were not statistically different for any of the selected ROIs. Mean values of right and left ADCave are reported as in Table 2. A good level of agreement was found between the two raters considering all ROIs, without significant bias or trends: the mean difference ± SD was 0.0005 ± 0.033 × 10^{-3} mm²/s; 95% limits of agreement were −0.065 × 10^{-3} to 0.066 × 10^{-3} mm²/s.

Group differences were detected in the ADCave values of the putamen and the SCPs (Table 2). Post hoc testing (Table 3 and Fig. 3A) revealed an increase in putaminal ADCave values in CBS and RS patients compared with both Parkinson’s disease patients and controls. Putaminal ADCave values did not distinguish CBS from RS.

ADCave values of the SCPs were significantly increased in RS patients compared with Parkinson’s disease patients and controls. In CBS patients, ADCave values of the SCPs were higher than in Parkinson’s disease and healthy controls, but the increase did not reach statistical significance. SCP ADCave values did not distinguish CBS from RS. Considering only putamen, the mean inter-rater difference ± SD was −0.0004 ± 0.020 × 10^{-3} mm²/s and 95% limits of agreement were −0.040 × 10^{-3} to 0.039 × 10^{-3} mm²/s, while for SCP the mean difference ± SD was −0.004 ± 0.039 × 10^{-3} mm²/s and 95% limits of agreement were −0.082 × 10^{-3} to 0.072 × 10^{-3} mm²/s.

We failed to detect a correlation between putaminal or SCP ADCave values of RS and CBS and any of the demographic or clinical parameters. No differences in ADCave values between groups were detected in the other ROIs analysed. The symmetry ratio of the various ROIs was similar in CBS, RS, Parkinson’s disease and control groups (data not shown).

**Histogram analysis**

The agreement between raters was even higher than that found in the ROI analysis, without significant bias or trends: the mean difference ± SD was 0.00005 ± 0.005 × 10^{-3} mm²/s and 95% limits of agreement were −0.010 × 10^{-3} to 0.010 × 10^{-3} mm²/s. Significant inter-group differences were found in the median ADCave for each cerebral hemisphere, and for the higher valued hemisphere, and in the hemispheric symmetry ratio (Table 2). The deep grey matter histograms disclosed lower basal ganglia symmetry ratios in CBS patients compared with other groups, but the difference failed to reach statistical significance (Table 2). Post hoc testing (Table 3) revealed that in CBS patients medians were significantly greater, in most cases on the left side. Comparing only the higher median between left and right hemispheres, higher values were found in CBS patients than in Parkinson’s disease or RS patients or in controls (Fig. 3C). In all CBS patients, the higher median ADCave value was found in the hemisphere contralateral to the most affected body side. The hemispheric symmetry ratio in CBS was lower than that in RS, Parkinson’s disease and healthy controls (Fig. 3D).

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**Table 2 ADCave values (×10^{-3} mm²/s) and symmetry ratios in the groups of subjects studied**

<table>
<thead>
<tr>
<th>ROIs</th>
<th>CBS</th>
<th>RS</th>
<th>Parkinson’s disease</th>
<th>Controls</th>
<th>p***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesencephalon ADCave</td>
<td>0.85 (0.77–0.88)</td>
<td>0.85 (0.82–0.88)</td>
<td>0.84 (0.80–0.85)</td>
<td>0.79 (0.78–0.83)</td>
<td>0.16</td>
</tr>
<tr>
<td>SCP ADCave</td>
<td>0.81 (0.78–0.83)</td>
<td>0.86 (0.83–0.88)</td>
<td>0.75 (0.71–0.80)</td>
<td>0.77 (0.72–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caudate ADCave</td>
<td>0.77 (0.74–0.79)</td>
<td>0.75 (0.73–0.78)</td>
<td>0.76 (0.75–0.78)</td>
<td>0.74 (0.72–0.79)</td>
<td>0.7</td>
</tr>
<tr>
<td>Putamen ADCave</td>
<td>0.77 (0.75–0.79)</td>
<td>0.75 (0.74–0.79)</td>
<td>0.72 (0.71–0.73)</td>
<td>0.70 (0.69–0.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pallidus ADCave</td>
<td>0.77 (0.76–0.79)</td>
<td>0.76 (0.74–0.78)</td>
<td>0.74 (0.72–0.75)</td>
<td>0.76 (0.67–0.80)</td>
<td>0.12</td>
</tr>
<tr>
<td>Thalamus ADCave</td>
<td>0.80 (0.78–0.83)</td>
<td>0.77 (0.75–0.80)</td>
<td>0.79 (0.77–0.80)</td>
<td>0.76 (0.73–0.78)</td>
<td>0.06</td>
</tr>
<tr>
<td>Internal capsule ADCave</td>
<td>0.70 (0.67–0.73)</td>
<td>0.71 (0.67–0.74)</td>
<td>0.69 (0.68–0.71)</td>
<td>0.72 (0.70–0.75)</td>
<td>0.35</td>
</tr>
<tr>
<td>Frontal WM ADCave</td>
<td>0.79 (0.77–0.82)</td>
<td>0.79 (0.77–0.82)</td>
<td>0.78 (0.76–0.79)</td>
<td>0.80 (0.78–0.81)</td>
<td>0.29</td>
</tr>
<tr>
<td>Parietal WM ADCave</td>
<td>0.85 (0.80–0.86)</td>
<td>0.80 (0.75–0.85)</td>
<td>0.80 (0.75–0.83)</td>
<td>0.80 (0.79–0.82)</td>
<td>0.19</td>
</tr>
<tr>
<td>Corpus callosum ADCave</td>
<td>0.80 (0.77–0.81)</td>
<td>0.83 (0.75–0.87)</td>
<td>0.83 (0.77–0.87)</td>
<td>0.82 (0.80–0.83)</td>
<td>0.36</td>
</tr>
<tr>
<td>Cerebral hemisphere histograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left median ADCave</td>
<td>0.94 (0.88–0.98)</td>
<td>0.87 (0.86–0.88)</td>
<td>0.89 (0.86–0.91)</td>
<td>0.88 (0.87–0.92)</td>
<td>0.01</td>
</tr>
<tr>
<td>Right median ADCave</td>
<td>0.92 (0.88–0.96)</td>
<td>0.87 (0.86–0.88)</td>
<td>0.89 (0.86–0.91)</td>
<td>0.89 (0.88–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Higher valued median ADCave</td>
<td>0.96 (0.89–0.98)</td>
<td>0.88 (0.86–0.89)</td>
<td>0.89 (0.86–0.92)</td>
<td>0.89 (0.88–0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemispheric symmetry ratio</td>
<td>0.968 (0.952–0.976)</td>
<td>0.993 (0.992–0.994)</td>
<td>0.991 (0.988–0.993)</td>
<td>0.990 (0.988–0.993)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep gray matter histograms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left median ADCave</td>
<td>0.81 (0.78–0.81)</td>
<td>0.78 (0.75–0.79)</td>
<td>0.78 (0.77–0.79)</td>
<td>0.77 (0.75–0.81)</td>
<td>0.62</td>
</tr>
<tr>
<td>Right median ADCave</td>
<td>0.82 (0.80–0.83)</td>
<td>0.78 (0.76–0.80)</td>
<td>0.77 (0.77–0.80)</td>
<td>0.78 (0.76–0.82)</td>
<td>0.25</td>
</tr>
<tr>
<td>Deep gray matter symmetry ratio</td>
<td>0.974 (0.963–0.989)</td>
<td>0.985 (0.983–0.987)</td>
<td>0.992 (0.988–0.997)</td>
<td>0.991 (0.990–0.992)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*p***Kruskal-Wallis test; P-values <0.05 were considered significant and are indicated in italics.

WM = white matter. Values are reported as median and interquartile range.
In CBS patients, the median cerebral hemisphere ADC\textsubscript{ave} values correlated with UPDRS (left: $r = 0.88$, $P = 0.008$; right: $r = 0.89$, $P = 0.06$; higher valued hemisphere: $r = 0.96$, $P < 0.001$). The higher valued median also correlated with H&Y stage ($r = 0.78$, $P = 0.04$). The hemispheric symmetry ratio correlated with both age ($r = 0.82$, $P = 0.02$) and age at onset ($r = 0.79$, $P = 0.04$).

**Sensitivity, specificity, PPV and NPV of ADC\textsubscript{ave} variables in the diagnosis of CBS, RS and Parkinson’s disease**

Considering the ROC curve analysis (Table 4), the increase in putaminal ADC\textsubscript{ave} differentiated CBS patients from Parkinson’s disease patients with high sensitivity, specificity, PPV and NPV, and RS patients from Parkinson’s disease patients with a slightly lower diagnostic capability. Putaminal ADC\textsubscript{ave} values could not distinguish between CBS and RS patients. The increased mean ADC\textsubscript{ave} values of SCP differentiated RS patients from Parkinson’s disease patients with high sensitivity, specificity and predictive values. However, SCP ADC\textsubscript{ave} values could not clearly distinguish CBS from RS and Parkinson’s disease.

On histogram analysis, the median ADC\textsubscript{ave} values in the higher valued hemisphere showed a high diagnostic capability in differentiating CBS from both Parkinson’s disease and RS patients, while the hemispheric symmetry ratio completely differentiated CBS from RS and Parkinson’s disease patients.

**Discussion**

In our study, putaminal ADC\textsubscript{ave} was significantly increased in both RS and CBS patients compared with Parkinson’s disease patients, whose ADC\textsubscript{ave} values were similar to those of healthy subjects. The increase in putaminal ADC\textsubscript{ave} was able to distinguish between CBS and Parkinson’s disease patients with high sensitivity (86%), specificity (92%), PPV (86%) and NPV (92%), and between RS and Parkinson’s disease patients (sensitivity 80%, specificity 77%, PPV 73%,

**Table 3** The DWI variables, among those reported in Table 2, that showed $P < 0.05$ on a Kruskal–Wallis test, underwent a post hoc analysis, using the Mann–Whitney U-test

<table>
<thead>
<tr>
<th>(K–W test: $P &lt; 0.05$)</th>
<th>CBS versus RS (P-value)</th>
<th>CBS versus Parkinson’s disease (P-value)</th>
<th>CBS versus controls</th>
<th>RS versus Parkinson’s disease (P-value)</th>
<th>RS versus controls (P-value)</th>
<th>Parkinson’s disease versus controls (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCP ADC\textsubscript{ave}</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>$&lt;0.001$</td>
<td>$&lt;0.001$</td>
<td>NS</td>
</tr>
<tr>
<td>Putamen ADC\textsubscript{ave}</td>
<td>NS</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Left hemispheric median ADC\textsubscript{ave}</td>
<td>0.005</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Right hemispheric median ADC\textsubscript{ave}</td>
<td>0.003</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Higher valued hemispheric median ADC\textsubscript{ave}</td>
<td>0.001</td>
<td>0.002</td>
<td>0.005</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hemispheric symmetry ratio</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

The threshold of significance, corrected for multiple comparisons, was set at $P < 0.0085$.

**Fig. 3** Scatterplot of ADC\textsubscript{ave} values of putamen (A), SCPs (B), median ADC\textsubscript{ave} in the higher valued hemisphere (C) and hemispheric symmetry ratio (D) in patients with CBS, RS, PD and healthy controls. Horizontal dotted lines indicate the median values.
Putaminal ADCave cut-off values were determined by ROC curve analysis. Hemispheric symmetry ratio studies (i.e. DWI acquisition parameters and ROI delineation) despite some methodological differences among different studies (i.e. DWI acquisition parameters and ROI delineation), ADC/ADCave values of the putamen have the best diagnostic accuracy in discriminating atypical parkinsonism from Parkinson’s disease but not among different forms of atypical parkinsonisms.

We found that RS patients had higher ADCave values at the level of decussation of the SCP than Parkinson’s disease patients, in line with a previous DTI study (Blain et al., 2006), but in our cohort of patients the increase in the mesencephalic ADCave failed to reach statistical significance. On the other hand, the ADCave values of SCPs in RS patients were significantly higher than those in Parkinson’s disease patients and controls. SCP ADCave values were able to differentiate RS from Parkinson’s disease patients with a sensitivity of 90% and a specificity of 85% but could not differentiate in CBS patients from RS patients.

The median hemispheric ADCave values in the higher valued side were greater in CBS patients than those in RS patients, Parkinson’s disease patients or healthy controls with very little overlap. The calculation of the hemispheric symmetry ratio—defined as the ratio between the smaller hemispheric median ADCave to the greater—allowed a complete differentiation of CBS from RS and Parkinson’s disease patients with a sensitivity, specificity, PPV and NPV of 100%. The differences found between CBS, RS and Parkinson’s disease patients in SCP and cerebral hemisphere median ADCave values and in the hemispheric symmetry ratio reflect differences in patterns of neurodegeneration. As showed by magnetic resonance (Soliveri et al., 1999; Groschel et al., 2004; Boxer et al., 2006; Whitwell et al., 2007; Josephs et al., 2008) and post-mortem studies (Hauw et al., 1994; Tsuboi et al., 2003), RS/PSP patients present atrophy of brainstem structures that are particularly severe in the midbrain and in the SCP. Cortical atrophy is in general limited to the premotor and supplemental motor areas in PSP patients (Josephs et al., 2006a). On the other hand, in CBS/CBD patients, there is a severe cortical involvement with atrophy affecting frontal, parietal and temporal regions (Soliveri et al., 1999; Dickson et al., 2000; Yekhlef et al., 2003; Groschel et al., 2004; Boxer et al., 2006; Josephs et al., 2006a) with a relative sparing of brainstem structures (Josephs et al., 2006a). This can explain the higher hemispheric right and left median ADCave values we found in CBS compared with RS although ADCave values in the deep grey matter of CBS and RS patients were not statistically different.

Conventional MRI showed a moderate to severe cortical atrophy in all our CBS patients (with a variable involvement of frontal, parietal and temporal lobe), but in only four of seven was an asymmetric pattern present (clearly so only in two patients). On the other hand, the ratio relative to the symmetry of global ADCave between the two hemispheres was reduced in all CBS patients who showed individual values below the normal range as well as below the lowest values found in either RS or Parkinson’s disease patients. This finding is consistent with the presence of typically asymmetric signs and symptoms in CBD (Lang et al., 1994; Kumar et al., 1998). Moreover, several neuroimaging studies of CBS patients have reported

### Table 4 Sensitivity, specificity and predictive values of DWI variables for the discrimination between CBS, RS and Parkinson’s disease

<table>
<thead>
<tr>
<th></th>
<th>Cut-off (×10⁻³ mm²/s)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putaminal ADCave</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBS versus Parkinson’s disease</td>
<td>0.745</td>
<td>86</td>
<td>92</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>RS versus Parkinson’s disease</td>
<td>0.735</td>
<td>80</td>
<td>77</td>
<td>73</td>
<td>83</td>
</tr>
<tr>
<td>SCP ADCave</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS versus Parkinson’s disease</td>
<td>0.815</td>
<td>90</td>
<td>85</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>Median ADCave in the higher valued hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBS versus Parkinson’s disease</td>
<td>0.925</td>
<td>86</td>
<td>85</td>
<td>75</td>
<td>92</td>
</tr>
<tr>
<td>CBS versus RS</td>
<td>0.895</td>
<td>100</td>
<td>90</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>Hemispheric symmetry ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBS versus Parkinson’s disease</td>
<td>0.9795</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CBS versus RS</td>
<td>0.981</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Cut-off values were determined by ROC curve analysis.
asymmetric cortical atrophy (Boxer et al., 2006; Koyama et al., 2007; Josephs et al., 2006a) and asymmetric hypometabolism or perfusion (Zhang et al., 2001; Ishii, 2002; Juh et al., 2005; Kreisler et al., 2005). Some MRI studies failed to detect asymmetric cortical involvement (Groschel et al., 2004) as we did in 3/7 of our CBS patients. This is not surprising as pathology affects both hemispheres in CBD and, in particular, late stages of the disease may be characterised by a similar extent of atrophy bilaterally. In our series of CBS patients, median ADC_ave values of both hemispheres were significantly increased compared with the values found in other groups, despite the presence of a clearly abnormal symmetry ratio, lending weight to this hypothesis.

In CBS patients, the median cerebral hemisphere ADC_ave values correlated with UPDRS and H&Y stage. This is likely due to the effect on whole hemispheric ADC_ave values of ADC_ave changes in deep brain structures: more severe neurodegeneration leads to higher ADC_ave and more severe extrapyramidal impairment. Interestingly, the hemispheric symmetry ratio was less abnormal in older patients with later age of onset, and a possible interpretation is that the physiological senile atrophy could attenuate the asymmetry of the pathologic atrophy.

In contrast to the results of the hemispheric ADC_ave histogram analysis, none of the ROIs selected in CBS patients showed an altered symmetry ratio. This could be due to a more marked asymmetry in the degree of neurodegeneration of hemispheric cortex than of basal ganglia, thalamus and white matter in CBS patients. However, it must be underlined that some methodological issues may be more relevant. For instance, ROI analysis is intrinsically affected by a greater variability compared with hemispheric histograms analysis (Mascalchi et al., 2005), which is almost completely operator-independent and is not influenced by partial volume effects. Indeed, histogram analysis of deep grey matter showed a clearly lower symmetry ratio in CBS patients than in other patient groups, but the reduction fell just short of a significant value (P = 0.056, Table 2) that could probably was obtained by a study with higher statistical power.

There is pathological (Dickson et al., 2000), imaging (Yamauchi et al., 1998; Groschel et al., 2004) and neurophysiological (Trompetto et al., 2003; Wolters et al., 2004) evidence of atrophy of the corpus callosum in CBD. As we acquired DW images only in the axial plane, we could only reliably assess ADC_ave values in the genu and splenium but not in the most affected middle region (Yamauchi et al., 1998), and we failed to detected differences between CBS patients and other groups. Consistently, structural MRI detected atrophy of the corpus callosum only in 3/7 of our CBS patients.

An important limitation of this study, and of other previous clinical–radiological studies, is that the recruitment criteria were only clinical (Gibb and Lees, 1988; Hughes et al., 1992; Lang et al., 1994; Litvan et al., 1996; Kumar et al., 1998) and, although we performed a thorough clinical follow up until 22 months after the scan, none of the patients studied had a pathological confirmation of their diagnosis. Patients with a clinical diagnosis of CBS may be affected not only by corticobasal degeneration but also by other tauopathies, such as PSP and Pick disease, or Alzheimer diseases or prion diseases (Josephs et al., 2004, 2006b). It has been shown that when PSP presents as CBS, this is in general due to either a concurrent cortical pathology from an additional process such as AD or from the primary pathology of PSP extending into cortical areas that are primarily and commonly affected in CBD (Tsuboi et al., 2005).

A differential diagnosis in vivo between the different forms of corticobasal syndromes is possible only for prion diseases, which may show characteristic clinical aspects and, above all, specific DWI abnormalities (Young et al., 2005), which were absent in all our CBS patients. As biochemical techniques have improved the ability to make a pathologic diagnosis, the gross anatomical findings on which clinical diagnoses are based have been found to be less specific. Predicting the biochemical abnormality may become increasingly important in view of current attempts to develop therapies, which modify the expression of soluble tau (Kertesz et al., 2003; Josephs et al., 2006b). Better clinico-radiological characterization of CBS and RS would aid the identification of tau-positive diseases.

In conclusion, DWI detected a significant increase in the median ADC_ave of cerebral hemispheres histograms in CBS patients compared with both RS and Parkinson’s disease patients. The calculation of the hemispheric symmetry ratio was able to discriminate all CBS patients from RS and Parkinson’s disease patients with a sensitivity and specificity of 100%. Our findings also confirmed that, via evaluation of putaminal ADC/ADC_ave values, DW imaging provides good discrimination between Parkinson’s disease and atypical parkinsonisms, including CBS.

The sample size of the patients included in this study was relatively small and patients’ disease duration was quite long. Further studies on larger samples and at earlier stages, and which correlate DWI with pathological data, will be needed to fully evaluate the capacity of DWI to discriminate between PSP and CBD.

References


