RESEARCH ARTICLE

Progression of Striatal and Extrastriatal Degeneration in Multiple System Atrophy: A Longitudinal Diffusion-Weighted MR Study

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ABSTRACT: Diffusion-weighted imaging has been largely used to detect and quantify early degenerative changes in patients with multiple system atrophy, but progression of neurodegeneration has been poorly investigated. We performed a serial diffusion-weighted imaging study in a population of multiple system atrophy patients and analyzed the evolution of diffusion properties in striatal and extrastriatal brain regions. Diffusion-weighted imaging was obtained in 11 multiple system atrophy patients at baseline and after a follow-up of 11.7 ± 1.2 months, and Trace (D) changes in different brain regions were correlated with disease duration and severity. A significant increase in Trace (D) was observed at follow-up in the putamen ($P < .001$), pons ($P = .003$), cerebellar white matter ($P = .03$), thalamus ($P = .013$), and frontal white matter ($P = .021$). Both Unified Multiple System Atrophy Rating Scale Part II and Unified Parkinson's Disease Rating Scale Part III scores significantly increased at follow-up ($P = .003$), but percent changes of Unified Parkinson's Disease Rating Scale Part III and Unified Multiple System Atrophy Rating Scale Part II did not correlate with percent changes of Trace (D) values in any brain region. This longitudinal study provides new insights into the progression of neurodegeneration in different brain regions in multiple system atrophy. Our results confirm that abnormal diffusivity in the putamen is sensitive to change over time in multiple system atrophy patients and show for the first time a progression of Trace (D) alterations in specific extrastriatal regions. Diffusivity changes in these regions may be useful for monitoring disease progression even after a short follow-up period.

Key Words: multiple system atrophy; diffusion-weighted imaging; longitudinal study

Multiple system atrophy (MSA) is an adult-onset sporadic disease clinically characterized by various combinations of parkinsonism, cerebellar dysfunction, and autonomic failure.[1] It can be classified into 2 main types, a parkinsonian variant (MSA-P) and a cerebellar variant (MSA-C), based on clinical presentation.[1] In MSA-P the nigrostriatal system is the site most affected, and degeneration may be less severe in the olivopontocerebellar system.[2,3] In MSA-C the olivopontocerebellar system is mainly involved, with loss of pontine neurons and transverse fibers, as well as atrophy of the middle cerebellar peduncles (MCPs).[2,3] Even if the designation *MSA-mixed* is no longer recommended by the second consensus statement,[4] it is a common observation that many MSA patients in the course of the disease develop a mixed phenotype.

Diffusion-weighted imaging (DWI) has been used to detect and quantify early neurodegenerative changes in patients with MSA.[5–8] This is a new nonconventional MRI technique highly sensitive to the microstructural

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integrity of cerebral white and gray matter. DWI measures the random movement of water molecules in tissues.[9,10] Neuropathological processes such as neuronal loss that destroy tissue architecture and remove some of the restricting barriers typically result in increased mobility of water molecules that can be measured as an increased apparent diffusion coefficient (ADC).[9,10]

Increased putaminal ADC separates MSA-P from Parkinson's disease (PD)[5] and increased ADC of the middle cerebellar peduncle differentiates MSA-P from both PD and progressive supranuclear palsy.[7] In a recent study, we showed that DWI changes are differently distributed in MSA-P and MSA-C, with higher Trace (D) values in the putamen and pons in MSA-P patients and in the cerebellum and MCP in MSA-C patients.[11] However, most previous studies showing DWI abnormalities in MSA used a cross-sectional design, and whether measurement of regional cerebral Trace (D) could serve as a quantitative marker for microstructural damage in the course of MSA remains to be further evaluated. To our knowledge, only 1 study has been performed to assess progression of neurodegeneration in MSA-P by serial DWI study.[12] This study suggested that abnormal diffusivity in the putamen is sensitive to change over time in MSA-P patients. Our aim was to perform a serial DWI study in a population of MSA patients and to analyze the evolution of diffusion properties in striatal and extrastriatal brain regions.

Patients and Methods

Subjects

We studied 11 probable MSA patients. Table 1 shows the demographic and clinical features of the patients at baseline. The diagnosis of MSA was made according to established criteria.[4] At baseline evaluation all MSA patients presented a mixed parkinsonian and cerebellar phenotype, 7 with predominant parkinsonism and 4 with predominant cerebellar features. All were clinically evaluated with the Unified Multiple System Atrophy Rating Scale (UMSARS) Part II (Motor Examination Scale)[13] and the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Motor Examination Scale). Each patient was scanned on 2 occasions within about a 1-year interval (mean ± SD, 11.7 ± 1.2 months; range, 9–13 months). Motor impairment was assessed on regular medication the same day of the MR DWI study. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of the Federico II University of Naples.

Magnetic Resonance Imaging

As previously described,[11] MRI was carried out with a 1.5-T MRI system (Gyroscan INTERA; Philips Medical System, Best, The Netherlands). The MRI protocol included high-resolution T1 (fast gradient-echo sequence: TR, 10 ms; TE, 2 ms; TI, 600 ms; 124 adjacent axial slices with a slice thickness of 1.2 mm; matrix 256 × 256) and DWI sequences (single-shot echoplanar imaging sequence: TE, 95 ms; TR, 7000 ms; 40 consecutive axial slices with a slice thickness of 3 mm; acquisition matrix, 128 × 128, which was interpolated to 256 × 256 during the calculation; acquisition time, 75 s). DWI scans were acquired with diffusion-sensitizing gradients switched in 3 orthogonal directions (slice, z; readout, x; phase encoding, y) and 3 b values (0, 500, and 1000 s/mm^2). The correction for eddy current distortions implemented in the Philips Gyroscan was applied to the DWI images. No correction for head movements was applied, but the lack of significant movement among the DWI series was checked visually in all subjects included in this study. From the mean diffusivity images, derived from the measurement of diffusivity in 3 orthogonal directions, diffusion Trace (D) brain maps were computed by commercially available Philips software.

TABLE 1. Demographic and clinical features of MSA patients at baseline

Male/female	5/6
Age at baseline (SD)	63.6 (10.1)
Disease duration, y ± SD	3.4 ± 1.1
Range, y	1–5
Predominant parkinsonian/cerebellar form	7/4
Parkinsonian features (n)	11
Autonomic features (n)	11
Cerebellar features (n)	11
Pyramidal features (n)	3

Data Analysis

The non-diffusion-weighted (b = 0 s/mm^2) images exhibiting a T2-contrast were spatially normalized into the Montreal Neurological Institute (MNI) space using the single-shot echoplanar imaging–derived template and the default spatial normalization settings (affine transformation with nonlinear components, voxel size of 2 × 2 × 2 mm) of SPM2 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The normalization parameters so calculated were then applied to the Trace (D) maps of each subject. The high-resolution T1-weighted volume was also spatially normalized into the MNI space using the T1-derived MNI template and the default parameters of SPM2. The spatially normalized non-diffusion-weighted (b = 0 s/mm^2) images, Trace (D) maps, and high-resolution T1-weighted images were processed for regions of interest (ROI) analysis using Anatomist software (http://brainvisa.free.fr). A template of ROIs (Fig. 1) was manually generated in the MNI space on the averaged T1 images obtained from controls, as previously

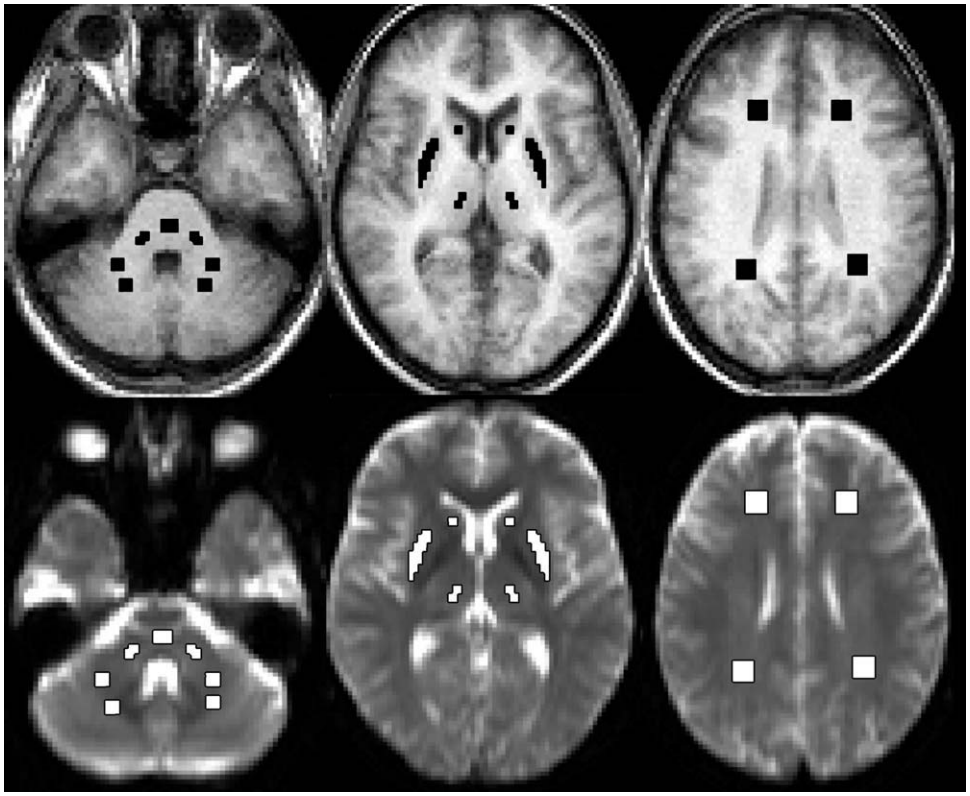

FIG. 1. Averaged axial T1 (**A**) and non-diffusion-weighted (b = 0 s/mm^2) (**B**) images obtained in controls at 3 different brain levels in the MNI space showing the location of the ROI template.

described.[11] Briefly, ROIs of fixed size were drawn bilaterally over consecutive slices (2 mm thickness) at specific Z levels in MNI space. Only in the pons was a single ROI drawn in each transaxial slice. For each brain region, mean Trace (D) was calculated by pooling all the ROIs defined in both hemispheres over consecutive transaxial slices. Regions so generated were: caudate nucleus, pons, middle cerebellar peduncles (MCPs), cerebellar white matter (CWM), and putamen. In addition ROIs were also defined over the frontal (FWM) and temporoparietal (TPWM) white matter and the thalamus. In each subject, the ROI template so generated was applied to spatially normalized T1, checked on the non-diffusion-weighted (b = 0 s/mm^2) images, manually adjusted if necessary and then automatically transferred to spatially normalized Trace (D) maps to determine the mean values in each brain region. To avoid CSF contamination within the brain regions, pixels with Trace (D) values higher than 2×10^{-3} mm^2/s were excluded (8).

Statistical Analysis

Data were tabulated and analyzed using SPSS 12.0 for Windows. Follow-up versus baseline comparison of UMSARS Part II, UPDRS Part III, and Trace (D) values was performed using the Wilcoxon signed-rank test. Correlation analysis between clinical variables and Trace (D) values at baseline and follow-up was performed using Spearman coefficients. The rate of progression of Trace (D) of each brain region was defined as the percent change between its Trace (D) values on baseline and follow-up scans. Correlation analysis between percent changes of UMSARS Part II and UPDRS Part III over the follow-up period and percent changes of Trace (D) values was performed using Spearman coefficients. In 4 of the 11 MSA patients, the cerebellar ROIs were not available because the cerebellar DWI sections were lacking.

TABLE 2. Progression of clinical and DWI parameters in MSA patients

	Baseline	Follow-up
UPDRS Part III, mean (range)	37.2 (23–59)	48.5 (26–73)[a]
UMSARS Part II, mean (range)	24.2 (14–35)	30.4 (18–41)[a]
Trace (D) values ($\times 10^{-3}$ mm^2/sec), mean ± SD		
Putamen	0.787 ± 0.079	0.856 ± 0.085[a]
Caudate	0.722 ± 0.071	0.771 ± 0.049
CWM	0.797 ± 0.095	0.816 ± 0.115[b]
Pons	0.783 ± 0.090	0.864 ± 0.117[a]
MCP	0.827 ± 0.079	0.879 ± 0.144
Thalamus	0.750 ± 0.023	0.793 ± 0.044[b]
FWM	0.793 ± 0.051	0.829 ± 0.076[b]
TPWM	0.802 ± 0.046	0.812 ± 0.050

CWM, cerebellar white matter; MCP, middle cerebellar peduncles; FWM, frontal white matter; TPWM, temporoparietal WM.
[a]$P < .001$,[b]$P < .05$, compared with baseline values

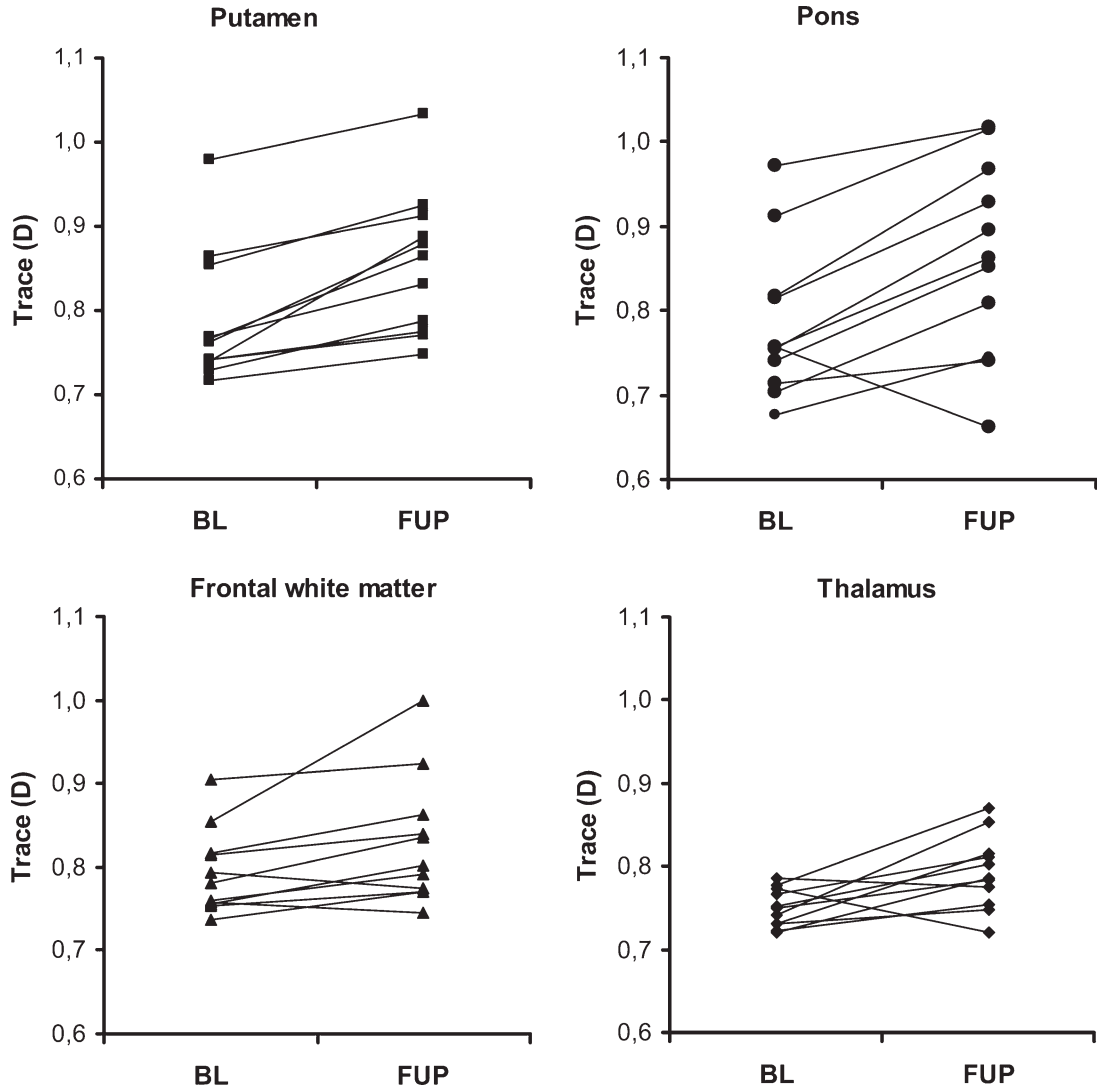

FIG. 2. Individual Trace (D) values in the putamen (**A**), pons (**B**), frontal white matter (**C**), and thalamus (**D**) at baseline and after 1 year of follow-up.

Results

Table 2 shows progression of clinical and DWI parameters in MSA patients. Both UMSARS Part II and UPDRS Part III scores significantly increased at follow-up ($P = .003$). The mean difference in UPDRS Part III score between baseline and follow-up was 11.4 points, corresponding to a 32% increase relative to baseline. The mean difference in UMSARS Part II score between baseline and follow-up was 6.2 points, corresponding to a 28.3% increase relative to baseline.

With regard to Trace (D) changes (Table 2), a significant increase was observed at follow-up in the putamen ($P = .003$), pons ($P = .01$), CWM ($P = .028$), thalamus ($P = .026$), and FWM ($P = .009$); see Table 2 and Figure 2. A higher rate of progression of Trace (D)—percent change versus baseline—was observed in the pons (10.2% ± 8.9%) and putamen (8.8% ± 5.2%); see Figure 3.

Percent changes of UPDRS Part III and UMSARS Part II and disease duration did not correlate with percent changes of Trace (D) in any brain region.

Discussion

This longitudinal study provides new insights into the progression of neurodegeneration in different brain regions in MSA. Over a relatively short period, we found a significant increase in diffusivity in the pons, putamen, cerebellar white matter, thalamus, and frontal white matter. A significant increase in putaminal diffusivity similar to that observed in our study was described in 10 MSA-P patients studied after a comparable mean follow-up period.[12] This finding probably reflect ongoing striatal degeneration and neuronal loss[2,3] and is in line with the significant progression of striatal volume loss reported in a longitudinal VBM study in MSA-P patients.[14]

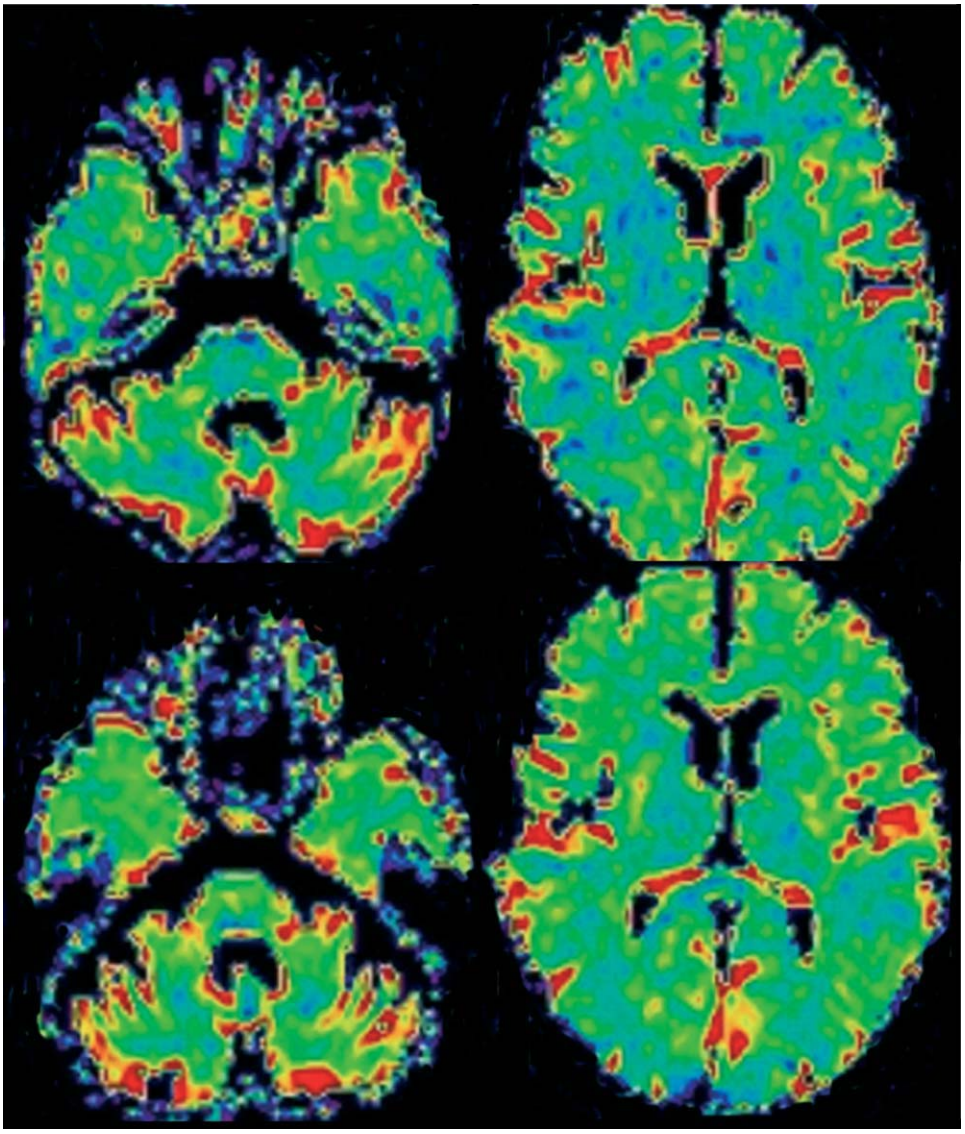

FIG. 3. Axial Trace (D) images spatially normalized into the MNI space obtained at the level of the cerebellum and the putamen in a patient at baseline (**A**) and at follow-up (**B**). Compared with baseline, the Trace (D) appeared to increase at the follow-up study, mostly in the pons and in the putamen. The trace (D) maps are scaled between a maximum value of 1.5 (red color) and a minimum value of 0.6 (blue color) × 103 mm^2/s. The trace (D) values above 2×10^{-3} mm^2/s have been masked (black color in the ventricles and CSF spaces).

This is the first study to investigate the progression of Trace (D) alterations over time in extrastriatal regions of MSA patients. Our findings probably reflect the ongoing degeneration in brain regions involved in neuropathological processes in MSA patients with a mixed phenotype. Previous cross-sectional studies from our group[11] and others[7,8,15] have reported increased Trace (D) in the pons, cerebellar white matter, and thalamus. The spatial topography of diffusivity changes in these regions parallels that of neuropathological alterations and/or in vivo brain volume loss previously reported in infratentorial and diencephalic regions.[16,17] Our results are in agreement and extend results of a longitudinal VBM morphometric study in MSA patients showing progression of brain atrophy in several cortical and subcortical gray matter regions including the cerebellum and the thalamus over a similar mean follow-up time.[14]

Increased diffusivity over time has never been described in frontal white matter of MSA patients. This finding is not surprising because the involvement of the frontal lobe in MSA has been suggested by recent postmortem studies and MRI and neuropsychological reports.[14,18,19] Diffuse infratentorial and supratentorial white matter pathological changes,[20] as well as increased frontal white matter MR diffusivity,[7] have been reported in MSA patients. Moreover, frontal gray matter atrophy and frontal cognitive impairment characterize MSA-C and MSA-P patients.[16,18,21] Consistent with our findings, Brenneis et al reported the progression of frontal gray matter atrophy in a longitudinal VBM study on MSA-P patients with a

similar follow-up period.[14] Because cognitive changes in MSA have been increasingly recognized and seem to be related to MSA progression,[18,21] it would be interesting to investigate possible relationships between frontal white matter Trace (D) changes and cognitive impairment in a further study.

The lack of significant correlations between the progression of diffusivity changes in the putamen and the progression of motor disturbances is in apparent contrast with the results of a previous study showing significant correlation between increase in putaminal Trace (D) values and UPDRS-III scores in parkinsonian MSA over a similar follow-up period.[12] This discrepancy may in part be explained by the inclusion of both MSA-P and MSA-C in our study, a difference with a previous report that included MSA-P patients only.[12] UPDRS may have a low sensitivity for evaluating complex motor picture in our patients presenting both extrapyramidal and cerebellar disturbances. In this respect, it is noteworthy that our results are in line with those of Brenneis et al, showing no significant correlation between the progression of basal ganglia volume loss and the worsening of UPDRS-III scores in MSA patients presenting cerebellar and parkinsonian features.[14] The lack of correlation between increase of UMSARS-II score and Trace (D) values in striatal and extrastriatal regions is less expected because UMSARS is a composite scale developed to capture the multiple aspects of MSA.[13] This result may be explained in different ways: possible variation between clinical and neuropathological presentation, the relatively small number of patients included in our study, and the short-follow-up period. Further studies in a larger number of patients with distinct clinical phenotypes and a longer follow-up period are required to address this issue.

A potential limitation of our study could be the lack of a longitudinal study in a control group to exclude possible age-related and repeatability-related biases on Trace (D) values.

Although age-related effects on regional brain diffusivity values cannot be excluded, these changes should be minor considering the brief follow-up period and could not explain our results. In our patients, Trace (D) changes during the mean 1-year follow-up period were more variable in direction and percentage (ie, −0.7% to 28.7% in the cerebellum; −2.3% to 17% in the FWM; −6.7% to 14.9 % in the thalamus; 3.9% to 19.9% in the putamen; −12.3% to 18.7% in the pons) than those expected for aging.[22–24] To our knowledge, longitudinal measures of cerebral regional Trace (D) values over a span of time similar to that of our study are not available in healthy controls. It is noteworthy, however, that no change in global diffusivity as measured by Trace (D) histograms was found in healthy controls over a period of about 2 years.[25] In addition, no significant putaminal changes were found in PD over a similar time range[12] or in Huntington's disease[26] during a 2-year follow-up. With regard to repeatability-related biases, in a previous study ADC values showed less than 5% fluctuation in healthy subjects examined for 5 times over different days,[22] supporting the opinion that the diffusivity changes observed in our patients are explained by interindividual DWI measure variability. Another issue could be the possible inclusion of patients with PD and/or idiopathic late-onset cerebellar ataxia. Although this cannot be completely excluded in the absence of a definite postmortem diagnosis of MSA, misdiagnosis is unlikely because all our patients met diagnostic criteria for probable MSA and had a mixed parkinsonian/cerebellar phenotype.

Despite these limitations, overall, the results of this preliminary study suggest that diffusivity in specific supratentorial and infratentorial regions is sensitive to change over time and might be an objective measure to monitor disease progression even after a short follow-up period.

The implication of these results for future therapeutic trials could be of potential interest. Using an approach similar to that used in previous reports on MRI atrophy rates in PSP, MSA-P, and Alzheimer's disease,[27,28] we calculated sample size estimates based on the rates of Trace (D) changes over 1 year and found that fewer MSA patients are required when using regions showing the most significant DWI changes (putamen/pons) rather than others (ie, for a drug effect equivalent to a 30% reduction in Trace [D] values, the number of patients required should be 80 of 176 for putamen/pons and 275 of 320 for thalamus/frontal white matter). However, the number of patients to be included in a trial might be lower if including only patients with MSA-P, as the main pathology of these patients is in the striatum. A limitation in determining sample size estimates in our study is the lack of control rates of Trace (D) changes over time in order to estimate the maximum treatment effect expected and to control for normal aging. Further work is required to better address this interesting issue. ■

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