Usefulness of combined fractional anisotropy and apparent diffusion coefficient values for detection of involvement in multiple system atrophy

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\textbf{Key words}: multiple system atrophy, Parkinson’s disease, fractional anisotropy values, apparent diffusion coefficient values, pons
Objective: To determine whether apparent diffusion coefficient (ADC) values and fractional anisotropy (FA) values can detect early pathological involvement in multiple system atrophy (MSA), and be used to differentiate MSA-P from Parkinson’s disease (PD).

Methods: We compared ADC and FA values in the pons, cerebellum and putamen of 61 subjects (20 probable MSA patients, 21 age-matched PD patients, and 20 age-matched healthy controls) using a 3.0T MR system.

Results: ADC values in the pons, cerebellum and putamen were significantly higher, and FA values lower in MSA than in PD or controls. These differences were prominent in MSA lacking dorsolateral putaminal hyperintensity (DPH) or hot cross bun (HCB) sign. In differentiating MSA-P from PD using FA and ADC values, we obtained equal sensitivity (70%) and higher specificity (100%) in the pons than in the putamen and cerebellum. In addition, all patients that had both significant low FA and high ADC values in each of these three areas were MSA-P cases, and those that had both normal FA and ADC values in the pons were all PD cases. Our diagnostic algorithm based on these results accurately diagnosed 90% of patients with MSA-P.

Conclusion: FA and ADC values could detect early pathological involvement prior to MR signal changes in MSA. Particularly, low FA values in the pons showed high specificity in discriminating MSA-P from PD. In addition, combined analysis of both FA and ADC values in all three areas was more useful than only one or the other.
Multiple system atrophy (MSA) is a sporadic adult-onset neurodegenerative disease presenting a combination of parkinsonism, cerebellar ataxia, and autonomic failure during the course of illness.[1-4] A consensus statement recommended designating patients as having MSA-P if parkinsonian features predominated, or MSA-C if cerebellar features predominated.[5] Differentiation of Parkinson’s disease (PD) from MSA-P is particularly important because these disorders differ in progression, prognosis, and treatment responses.[6] However, a purely clinical differentiation, especially in the early phase of disease, remains challenging.

In advanced MSA, magnetic resonance imaging (MRI) reliably shows characteristic signal changes such as dorsolateral putaminal hyperintensity (DPH) and the hot cross bun (HCB) sign,[7-10] but these signs are not useful for differentiation between MSA-P and PD in their early phases.[11]

Apparent diffusion coefficient (ADC) values and fractional anisotropy (FA) values are new parameters on MRI, and these were used to evaluate the degree of tissue degeneration in various disorders. ADC values measure the average water diffusion, and increasing ADC values indicate tissue degeneration. FA values measure the degree of anisotropy of the diffusing water along different axes of the image, and decreasing FA values represent tissue degeneration. Recently, there are some reports concerning ADC and FA values in MSA-P and PD patients. ADC values in the striatum were higher in MSA-P than in PD,[12] and those in the basis pontis and cerebellum were higher in MSA-C than in controls.[13] FA values in the middle cerebellar penduncle, basis pontis and internal capsule were lower in MSA-C than in controls.[14] However, these results still do not conclude whether ADC and FA values are really effective at discriminating MSA-P from PD, particularly in their early phase. To confirm the hypothesis that ADC and FA values can detect abnormalities in patients with MSA even without DPH and HCB and discriminate MSA-P from PD, a direct study of these values at various stages of MSA and PD in various regions is needed.

The object of the present investigation is to examine the utility of ADC and FA values in the pons, cerebellum and putamen to detect not only the early pathological changes in MSA but also to differentiate MSA-P from PD.

Patients and methods
We studied 61 subjects (20 consecutive patients with probable MSA (10 MSA-C; 10 MSA-P), 21 age- and gender-matched patients with probable PD, 20 age- and gender-matched healthy volunteers) (table 1). There was a significant difference in the duration from initial symptoms to MRI evaluation between MSA (4±2 years, range 1 to 10 years) and PD (10±8 years, range 1 to 30 years) patients. Furthermore, MSA-P and PD patients measured the Hohen-Yahr (H-Y) score. There was no significant difference in the H-Y score between MSA-P (3.6±1.0) and PD (3.5±1.0) patients. Patients in relatively early stage of MSA were included in this study. Clinical diagnoses of MSA[5] and PD[15] were established by consensus diagnostic criteria. All MSA patients fulfill clinically probable criteria. In addition, Controls underwent the same MRI examination. Informed consent was established before subject participation. This study was approved by the ethics committee of the Nagoya University Graduate School of Medicine.

MRI protocol

All scanning was carried out with a 3.0T MR scanner (Trio, Siemens, Erlangen, Germany), using a receive-only 8-channel phased-array head coil. DWI was obtained with optimal methods[16] using a Stejskal-Tanner sequence with single-shot spin-echo-type echo-planar imaging, flip angle of 90°, and a repetition time of 7700 ms. Echo times corresponding to respective b-factors were 75 ms for 700 s/mm². Echo spacing was 0.79 ms, and matrix size was 128×128 with a readout bandwidth of 1562 Hz/pixel. Sixty axial slices, 2 mm thick with a 0.6-mm interslice gap, were used to image the entire brain with a 23-cm square field of view.

A motion-probing gradient (MPG) was applied in 6 orientations after acquisition of b=700 images. The 128×128 data matrix was zero-fill interpolated to 256×256. An acceleration factor of two was applied using the parallel imaging technique, generalized autocalibrating partially parallel acquisitions (GRAPPA).[17] which is an extension of the simultaneous acquisition of spatial harmonics technique. Eddy current-related geometric distortions were not prominent between the images of each MPG directions; thus, distortion correction post-processing was not applied.

Data analyses

ADC and FA values, and tractography were obtained using the public domain software
dTV II for DWI analysis developed by the Imaging Computing and Analysis Laboratory, Department of Radiology, University of Tokyo Hospital, Japan, and made available via the URL http://www.utradiology.umin.jp/people/masutani/dTV.htm. Regions of interest (ROI) in the pons and cerebellum were placed within closed curves drawn around the entire axially imaged pons and around the axial cerebellum section that showed the largest dentate nucleus profile (fig. 1A, 1B). Since it was difficult to discriminate the entire axial putamen on MRI, ROIs in the putamen were placed within closed fixed-circles drawn on the axial putaminal section (fig. 1C). Regional ADC and FA values were calculated in each ROI. Mean ADC and FA values were adapted as representative indices of ADC and FA values. For tractography visualization in the pons and cerebellum which could be anatomically analyzed in their entirety, seed areas were defined on T2-weighted axial images (b=0) as the interior of the previously mentioned closed curve drawn around the pons and cerebellum. The presence or absence of HCB or DPH signs[18] was determined on T2-weighted axial images of the pons or putamen by the radiologist.

Statistical analyses were performed using SPSS 11.0 for Windows (SPSS Inc, USA). The Kruskal-Wallis test was used for comparison of ADC or FA values among MSA, PD, and controls or MSA-P, PD, and controls. The significance level was set at p<0.05. In addition, to differentiate probable MSA-P from PD, we performed receiver operating characteristic (ROC) -analysis for FA and ADC values in each ROI. Based on these ROC-data, we set cutoff points for FA and ADC values, respectively.

Results

Features of tractography

Tractography in representative MSA, PD and control subjects are shown in Figure 2. Compared with PD and control, MSA showed decreased volume of fiber bundles corresponding anatomically to the middle cerebellar peduncle, transverse pontine and pyramidal tract fibers located in the pontine ROI, and also to the middle cerebellar peduncle and frontocerebellar tract located in the cerebellar ROI. No marked difference was seen between PD and controls. Although these fiber bundle losses were prominent in most MSA patients, some MSA had relatively well preserved tractography.
**FA and ADC values in the pons, cerebellum and putamen**

FA values in the pons, cerebellum and putamen in MSA were significantly lower than those in PD or controls. With respect to MSA phenotype, FA values in all three areas were significantly lower in MSA-P and MSA-C than in either PD or controls (fig.3A-C). However, the FA values in the pons and cerebellum tended to be lower in MSA-C than in MSA-P, but the differences were not significant. FA values in the putamen were similar in MSA-C and MSA-P subjects.

ADC values in the pons, cerebellum and putamen were significantly higher in MSA than in PD or controls. With respect to MSA phenotype, ADC values in all three areas were significantly higher in MSA-P or MSA-C than in PD or controls (fig.4A-C), while ADC values in the pons and cerebellum tended to be higher in MSA-C than in MSA-P, but the difference was not significant. ADC values in the putamen were similar in MSA-C and MSA-P.

Statistically, lower FA and higher ADC values in the pons and cerebellum were more prominent than those in the putamen.

**FA and ADC values in MSA with or without MR signal changes**

In our MSA patients, specificity of the HCB and DPH signs were both 100%, while sensitivity of the HCB and DPH signs were only 45.0% and 40.0%, respectively. However in 11 MSA patients without the HCB sign, 8 (72.7%) showed low FA values in the pons, 7 (63.6%) in the cerebellum, and 6 (54.5%) in the putamen, and 8 (72.7%) showed high ADC values in the pons, 6 (54.5%) in the cerebellum, and 8 (72.7%) in the putamen (table 2). In 12 MSA patients without the DPH sign, 10 (83.3%) showed low FA values in the pons, 10 (83.3%) in the cerebellum and 10 (83.3%) in the putamen, and 8 (66.7%) showed high ADC values in the pons, 9 (75.0%) in the cerebellum and 6 (50.0%) in the putamen (table 2). These observations demonstrate that changes in FA and ADC values can be detected prior to the appearance of HCB and DPH sign in early phase MSA. FA values were significant lower in MSA patients without DPH or HCB sign than PD patients. Likewise ADC values were significant higher in MSA patients without DPH or HCB sign than PD patients.

**Differentiating MSA-P from PD**
To differentiate probable MSA-P from PD, we performed ROC-analysis. Based on these ROC-data, we set cutoff points for FA values in the pons, cerebellum and putamen at 0.38, 0.30 and 0.35, and for ADC values at 0.98, 0.96 and 0.83, respectively, and that both sensitivity and specificity were as high as possible in our cases. Sensitivity and specificity based on these cutoff points for FA values are 70.0% and 100.0% in the pons, 70.0% and 63.6% in the cerebellum, 70.0% and 87.5% in the putamen (fig.5). Sensitivity and specificity based on these cutoff points for ADC values are 70.0% and 70.0% in the pons, 60.0% and 87.5% in the cerebellum, 70.0% and 63.6% in the putamen (fig.5). FA values in the pons were particularly useful for readily differentiating MSA-P from PD, and provided equal sensitivity and higher specificity than those in the cerebellum and putamen. Hence, pontine FA values were especially useful markers to diagnose MSA-P as well as those in the cerebellum and putamen.

In addition, our results showed that 3 MSA-P patients had low FA but normal ADC values (fig.5A red area), and 3 had normal FA but high ADC values (fig.5A blue area) in the pons. In the cerebellum and putamen (fig.5B and C), 2 and 2 MSA-P patients, respectively, had low FA but normal ADC values, and 1 and 2, respectively, had normal FA but high ADC values.

All patients that had both low FA and high ADC values in each of the three areas were probable MSA-P cases, (fig.5A-C, purple areas) suggesting that patients with such values have a high possibility of being correctly diagnosed as MSA-P. Furthermore, no MSA cases had both normal FA and ADC values in the pons (fig.5A, white area), and all patients that had both normal FA and ADC values in the pons were PD cases. However, in the cerebellum and putamen (fig.5B and C white areas), 2 and 1 MSA-P cases, respectively, had both normal FA and ADC values. Hence, it was more useful to examine both FA and ADC values than only one or the other to distinguish MSA-P from PD.

Therefore, based on these results, we devised an algorithm for differentiating probable MSA-P from PD (fig.6). Using this algorithm in our 31 cases (PD: 21, probable MSA-P: 10), all patients that had both normal FA and ADC values in all three areas were PD cases (12 PD cases). In addition, all patients that had both low FA and high ADC values in any of the three areas were probable MSA-P cases (9 probable MSA-P cases). Taken together, the “MSA area” included 90.0% of probable MSA-P cases and
no PD cases, and the “PD area” included 57.1% of PD cases and no probable MSA-P cases.

Discussion

This is, to our knowledge, the first systematic study to demonstrate a beneficial utility of simultaneous assessment of ADC and FA values on multiple regions including the pons, cerebellum and putamen in MSA, PD, and controls. We showed that low FA and high ADC values in these regions were significant even in MSA cases without HCB or DPH signs, suggesting that FA and ADC assessment can be a potent procedure to detect early involvement in MSA without diagnostic MRI findings. In particular, 90.0% of probable MSA-P cases showed a combination of low FA and high ADC values in one or more of the three areas, but no PD patients showed both low FA and high ADC values in any of the three areas. In addition, 57.1% of PD cases showed a combination of normal FA and ADC values in all three areas. These results suggest that combined evaluation of FA and ADC values in early disease stages provides an accurate method for differentiating MSA-P from PD.

ADC values measure the average water diffusion. High putaminal ADC values were reported to be helpful in differentiating MSA-P from PD.[12] Subsequently, brainstem ADC values in MSA-C were demonstrated to be increased.[13] Since increases in ADC values have been shown in certain other diseases[19-21] and in normal aging,[22] high ADC values are thought to reflect destruction of tissue architecture. In contrast, FA values are new parameters specifically measuring the degree of anisotropy of the diffusing water along different axes of the image, enabling useful quantitative estimation of decreased tissue anisotropy reflecting degeneration. Reduced FA values have been reported in certain other diseases[23-25] and in normal aging.[26] More recently, decreased FA values in cerebellopetal fibers and pyramidal tracts have been reported in MSA-C,[14] and low FA values are also thought to reflect destruction of tissue architecture. In this study, we demonstrated that by using small voxels and optimized parameters[16] as well as a GRAPPA[17] algorithm for suppressing artifact and noise to obtain reliable ADC and FA values as evidenced by clear tractography results, increased ADC and decreased FA values could reflect destruction of brainstem, cerebellar or putaminal tissue architecture resulting from neuronal loss and/or gliosis,
enhancing random mobility of free water molecules within the tissue. Our results support previous observations and extend the significance of FA and ADC values in the diagnosis of MSA-P, even cases without DPH or HCB signs.

Some of our MSA-P or PD cases showed a combination of normal FA but high ADC or low FA but normal ADC values in various regions. As above, high ADC and low FA values could reflect a similar destruction of tissue architecture and have been demonstrated in various pathological changes including brain atrophy, atherosclerotic change and normal aging.[22, 26] However, these parameters are based on different pathological conditions. This may be one of the reasons why some cases showed normal FA but high ADC or low FA but normal ADC values. Furthermore, only cases of MSA-P had both low FA and high ADC values in each of the three areas. FA and ADC values may mutually provide additional information about the evolution of the disease that is not available from one method. These findings suggest that the combined evaluation of FA and ADC values could be more useful for early detection of pathological involvement in MSA-P, than the evaluation of either of these separately.

With respect to locations, pontine FA and ADC values were especially useful markers to diagnose MSA-P compared to those in the cerebellum and putamen. Though degeneration of olivopontocerebellar systems is evident from clinical features and MRI findings in MSA-C, these changes are not apparent in the early phase of MSA-P. The present study clearly demonstrated that even though reductions in FA values and increases in ADC values in the pons and cerebellum were more remarkable in MSA-C than in MSA-P, these changes still were highly evident in MSA-P. The question arises as to why significantly abnormal ADC and FA values can be seen in the pons even in early phase MSA. Early stage patients with MSA in Caucasian populations have been reported to show selective neuronal cell loss in the substantia nigra and locus coeruleus, with relative sparing of both the striatum and the olivoponto-cerebellar system.[27] One possible explanation may be that ADC and FA values have the potential to detect minimal and subclinical, but accumulated, neurodegeneration in the pons, because the pons contains the neurons and fiber tracts (e.g., the pontine nuclei, transverse pontine fibers, and corticospinal tracts) that are preferentially effected in MSA, and thus, could accumulate and reflect the MSA specific neurodegenerative process at an early phase of illness. Alternatively, it could be due to differences in the pathological features of MSA.
among Japanese and Caucasian populations. We previously reported that MSA-C was
more frequent, and MSA-P less frequent in Japanese populations[11] as compared to
Western populations,[3] and also that proton MR spectroscopy (1H-MRS) showed
significantly lower N-acetylaspartate/creatine ratios in the basis pontis suggesting
more neuro-axonal loss or dysfunction in MSA-P than in PD.[28] The
olivoponto-cerebellar system shows more profound degeneration in Japanese MSA-P.
While further study is needed to address this issue, we suggest that the pons is a
beneficial region to detect early pathological change in MSA.

In previous reports,[12] ADC values in the dorsolateral putaminal ROIs were reported
to be more useful to distinguish MSA from PD compared to those in the anteroventral
one. It is interesting that this result well corresponded to the spatial distribution of
pathological lesion in the putamen in MSA. On the contrary, we used relatively lager
size of ROIs than previous reports to obtain the reliable data under our MRI conditions
such as higher magnetic field strength, specific analyzing soft and parameters. In
addition, since some MSA and PD patients showed obscure putaminal edges on MRI,
we set the ROIs in the relatively midst putamen including dorsolateral parts. These
specific MRI conditions may have caused the differences of the sensitivity and
specificity in the putamen between our study and previous one. These discrepancies
might be also explained by ethnic difference that olivoponto-cerebellar system could be
more severely affected in Japanese than Western people. Multicenter survey will be
needed to clarify the optimized size of ROIs, magnetic field strengths, and parameters to
standardize the FA and ADC values as diagnostic criteria.

In summary, combined evaluation of FA and ADC values in the putamen, cerebellum
and putamen would provide useful information for highly and accurate differentiation
MSA-P from PD. Such early FA reduction and ADC increase are likely to be associated
with subtle early degenerative processes in MSA even without diagnostic MR signal
abnormalities. In addition, it will be necessary to apply this algorithm for possible MSA
patients without diagnostic MRI findings and to determine whether these patients will
develop full-blown MSA symptoms in several years in a prospective manner to justify
our conclusion.

Competing interests: none declared
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Figure legends

Figure 1: Regions of interest (ROI)
Regions of interest (ROI) in the pons (A), cerebellum (B) and putamen (C).

Figure 2: Tractography in the pons and cerebellum
A: Pons. Visualization of fibers in the pons and pyramidal tract fibers is unclear in MSA.
B: Cerebellum. Visualization of transverse fibers proceeding via the middle cerebellar peduncle, and of fibers connecting to the frontal lobe is unclear in MSA.

Figure 3: FA values in the pons, cerebellum and putamen
FA values in MSA-C, MSA-P, PD and controls are shown in the pons (A), cerebellum (B) and putamen (C). *: p<0.001, **: p<0.005, ***: p<0.01, ****: p<0.05
FA values in all three areas were significantly lower in MSA-P and MSA-C than in either PD or controls.

Figure 4: ADC values in the pons, cerebellum and putamen
ADC values (x10^-3mm²/s) in MSA-C, MSA-P, PD and controls are shown in the pons (A), cerebellum (B) and putamen (C). *: p<0.001, **: p<0.005, ***: p<0.01, ****: p<0.05
ADC values in all three areas were significantly higher in MSA-P or MSA-C than in PD or controls.

Figure 5: Differentiation of MSA-P from PD
FA and ADC values in the pons (A), cerebellum (B) and putamen (C). In the pons, cerebellum, and putamen, the cutoff point was set at 0.38, 0.30, 0.35 for FA, and 0.98, 0.96, 0.83 for ADC. Sensitivity/ specificity to differentiate probable MSA-P from PD using these cutoff points were shown.
FA values in the pons were particularly useful for readily differentiating MSA-P from PD. In addition, some MSA-P cases had low FA and normal ADC values or normal FA and high ADC values. All patients that had both low FA and high ADC values in all three areas were MSA cases, and all patients that had both normal FA and ADC values
in the pons were PD cases.

Figure 6: Algorithm for differentiating probable MSA-P from PD using FA and ADC values

Using this algorithm in our 31 cases (PD: 21, probable MSA-P: 10), the “MSA area” included 90% of probable MSA-P cases and no PD cases, and the “PD area” included 57.1% of PD cases and no MSA-P cases.
References


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Table 1: Patients data

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<th>Number of cases</th>
<th>Age (years)</th>
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<th>Duration (years)</th>
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<td>20</td>
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<td>MSA-P</td>
<td>10</td>
<td>63±11</td>
<td>4/6</td>
<td>4±3</td>
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<td>MSA-C</td>
<td>10</td>
<td>58±7</td>
<td>4/6</td>
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<tr>
<td>PD</td>
<td>21</td>
<td>62±11</td>
<td>13/8</td>
<td>10±8</td>
<td>3.5±1.0</td>
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<tr>
<td>Control</td>
<td>20</td>
<td>62±11</td>
<td>13/7</td>
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</table>

MSA; multiple system atrophy, MSA-P; multiple system atrophy predominated in parkinsonism, MSA-C; multiple system atrophy predominated in cerebellar ataxia, PD; Parkinson's disease, H-Y; Hohen-Yahr score
<table>
<thead>
<tr>
<th>ROI</th>
<th>Cutoff points</th>
<th>In 12 MSA patients without DPH sign</th>
<th>In 11 MSA patients without HCB sign</th>
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<tr>
<td>Pons</td>
<td></td>
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<tr>
<td>FA ≤ 0.38</td>
<td>10 (83.3%)</td>
<td>8 (72.7%)</td>
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</tr>
<tr>
<td>ADC ≥ 0.98</td>
<td>8 (66.7%)</td>
<td>8 (72.7%)</td>
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<td>Cerebellum</td>
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<td>FA ≤ 0.30</td>
<td>10 (83.3%)</td>
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<td>7 (63.6%)</td>
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<tr>
<td>ADC ≥ 0.96</td>
<td>9 (75.0%)</td>
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<td>Putamen</td>
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<td>FA ≤ 0.35</td>
<td>10 (83.3%)</td>
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<td>6 (54.5%)</td>
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<tr>
<td>ADC ≥ 0.83</td>
<td>6 (50.0%)</td>
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<td>8 (72.7%)</td>
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</table>

MSA; multiple system atrophy, FA; fractional anisotropy values, ADC; apparent diffusion coefficient values, ROI; regions of interest, DPH; dorsolateral putaminal highintensity, HCB; hot cross bun
Figure 1
Figure 2A

Control

PD

MSA
Figure 2B

Control

PD

MSA
Figure 3

A

FA in pons

MSA-C  MSA-P  PD  control

0.30  0.40  0.50

B

FA in cerebellum

MSA-C  MSA-P  PD  control

0.20  0.30  0.40

C

FA in putamen

MSA-C  MSA-P  PD  control

0.30  0.40  0.50
Figure 4

A

B

C

ADC in pons (×10⁻³ mm²/s)

ADC in cerebellum (×10⁻³ mm²/s)

ADC in putamen (×10⁻³ mm²/s)

MSA-C  MSA-P  PD  control

MSA-C  MSA-P  PD  control

MSA-C  MSA-P  PD  control
Figure 5

A

<table>
<thead>
<tr>
<th>ADC in pons (x10^-3 mm^2/s)</th>
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<tr>
<td>0.50</td>
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<tr>
<td>1.00</td>
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<td>1.50</td>
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FA in pons
FA≤0.38: 70.0 / 100.0
ADC≥0.98: 70.0 / 70.0

B

<table>
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<th>ADC in cerebellum (x10^-3 mm^2/s)</th>
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<tbody>
<tr>
<td>0.50</td>
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<tr>
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<td>1.50</td>
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</table>

FA in cerebellum
FA≤0.30: 70.0 / 63.6
ADC≥0.96: 60.0 / 87.5

C

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<tr>
<td>0.50</td>
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<tr>
<td>1.00</td>
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<td>2.00</td>
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</table>

FA in putamen
FA≤0.35: 70.0 / 87.5
ADC≥0.83: 70.0 / 63.6

Cutoff points: sensitivity / specificity
Figure 6
Algorithm for differentiating MSA-P from PD using FA and ADC values

Normal FA and ADC values in all three areas

Yes

PD

n = 31
MSA-P = 10
PD = 21

No

Low FA and high ADC values in any of the three areas

n = 19
MSA-P = 10
PD = 9

No

PD / MSA-P

n = 12
MSA-P = 0
PD = 12

Yes

MSA-P

n = 9
MSA-P = 9
PD = 0