Decreased Striatal Monoaminergic Terminals in Olivopontocerebellar Atrophy and Multiple System Atrophy Demonstrated with Positron Emission Tomography

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We used [11C]dihydrotetrabenazine, a new ligand for the type 2 vesicular monoamine transporter (VMAT2), with positron emission tomography to study striatal monoaminergic presynaptic terminals in 4 patients with multiple system atrophy, 8 with sporadic olivopontocerebellar atrophy, and 9 normal control subjects. Specific binding in the striatum was significantly reduced in the multiple system atrophy patients as compared with the normal control group, with average reductions of 61% in the caudate nucleus (p = 0.002) and 58% in the putamen (p = 0.009). Smaller reductions were found in the sporadic olivopontocerebellar atrophy group, averaging 26% in the caudate nucleus (p = 0.05) and 24% in the putamen (p = 0.11). Mean blood-to-brain [11C]dihydrotetrabenazine transport (Kt) was significantly different between groups only in the cerebellum, with values for the sporadic olivopontocerebellar atrophy group diminished compared with the normal control group. Cerebellar Kt was not significantly decreased in the multiple system atrophy group. The finding of reduced striatal VMAT2 in sporadic olivopontocerebellar atrophy patients suggests nigrostriatal pathology, indicating that some may later develop symptomatic extrapyramidal disease.


Multiple system atrophy (MSA) is a progressive neurological disorder consisting of combinations of extrapyramidal, pyramidal, cerebellar, and autonomic symptoms and signs [1-7]. The term "possible MSA" is used for patients with only extrapyramidal symptoms that are poorly responsive or unresponsive to levodopa (striatoniigral degeneration [SND]) and patients with a combination of cerebellar ataxia and extrapyramidal symptoms [2]. The term "probable MSA" pertains to patients with extrapyramidal symptoms poorly responsive or unresponsive to levodopa accompanied by autonomic symptoms with or without pyramidal and cerebellar symptoms (Shy-Drager syndrome [SDS]) [2]. Similarly, the term "probable MSA" is applied to patients with cerebellar and autonomic symptoms with or without extrapyramidal and pyramidal symptoms [2]. The diagnosis of "definite MSA" requires a typical history and physical findings with subsequent postmortem verification [2]. In most patients with definite MSA, neuropathological examination demonstrates degenerative changes in the cerebellum and brainstem as well as the basal ganglia and spinal cord [8]. The neuropathological changes in MSA include those seen with SND [9-12], SDS [3, 13-16], and olivopontocerebellar atrophy (OPCA) [3, 6-8]. Neuronal loss and gliosis occur in the basal ganglia (putamen and globus pallidus), brainstem and cerebellum (substantial nigra, locus ceruleus, dorsal vaginal nuclei, vestibular nuclei, inferior olives, pontine nuclei, and cerebellar Purkinje cells), and spinal cord (pyramidal tracts, intermediolateral columns, and Onuf's nuclei) [1, 7, 8]. Recently, oligodendrogial [17-21] and neuronal [22-24] intracytoplasmic and intranuclear inclusions were observed with MSA.

OPCA is a neurodegenerative disorder occurring...
both sporadically (sOPCA) and with dominant (dOPCA) and recessive (rOPCA) forms of hereditary transmission and characterized by progressive ataxia of gait and speech, disturbances of extracocular movements, and difficulty with limb coordination [25–29]. The neuropathological changes include loss of inferior olivary neurons and their climbing fiber projections to the cerebellum, decreased numbers of pontine neurons and their mossy fiber connections in the cerebellum, and marked reduction of Purkinje cells and granule cells [7, 30–32]. Some patients initially diagnosed with sOPCA develop additional clinical signs characteristic of MSA, and at postmortem show degenerative changes not only within the brainstem and cerebellum, but also within the basal ganglia and spinal cord [1–4]. Most patients who present initially with OPCA and later develop clinical manifestations of MSA have the sporadic and not the hereditary form of the disorder [2]. The percentage of patients with sOPCA who later develop MSA is unknown, and no method is currently available to determine whether individual sOPCA patients will progress to develop MSA. Decreased striatal function that is not accompanied by clinical evidence of extra-pyramidal disease might be expected in sOPCA patients who will develop MSA with time. A means of detecting striatal abnormalities in sOPCA patients would serve a useful function in permitting the distinction of “pure” OPCA and MSA earlier in their courses and thus in assisting with the prognosis of the disorder. The present investigation was designed to determine whether positron emission tomography (PET) might be used to detect abnormalities in striatal monoaminergic presynaptic terminals in patients with sOPCA.

Several radiopharmaceuticals have been utilized previously with PET to examine monoaminergic presynaptic terminals, but medication use and compensatory effects of disease processes affect the results. Recently our center developed [1-12] dihydrotetrabenazine (DTBZ) to examine the density of binding to the type 2 vesicular monoamine transporter (VMAT2). Studies in animals suggested that this agent avoids the problems from disease-related compensation or medications encountered with previously used agents [33–35]. In the present study and a companion investigation [35], this new ligand was utilized to determine whether the density of monoaminergic terminals in the striatum is decreased with normal aging and in Parkinson’s disease, in MSA, and in at least some patients with sOPCA. A preliminary version of the present study has been published [36].

Materials and Methods

Patient Groups and Normal Subjects

The Institutional Review Board approved the studies, and we obtained informed consent from each subject. Three groups were studied: 4 patients with probable MSA (age 71 ± 9 years, mean ± standard deviation), 8 patients with sOPCA (age 55 ± 9 years), and 9 normal control subjects (age 58 ± 10 years). The normal control subjects were selected on the basis of age from a larger group reported in the accompanying investigation, and included all subjects in the middle-age and elderly groups [35]. The control subjects had no history of neurological disorders and no abnormalities on general physical and neurological examinations. None of the patients or control subjects were receiving centrally active medications that influence studies of striatal VMAT2 binding (Table 1).

We studied 4 patients with probable MSA (see Table 1). The diagnosis of MSA was based on the demonstration of an extrapyramidal disorder with autonomic failure unresponsive or poorly responsive to levodopa (Patients 1 and 4, see Table 1) or a levodopa-unresponsive extrapyramidal disorder with autonomic failure and cerebellar dysfunction (Patients 2 and 3, see Table 1). The signs of disorders of extrapyramidal, cerebellar, and autonomic function were graded clinically as mild, moderate, or severe (see Table 1). We defined an extrapyramidal movement disorder as the presence of at least two of the following: akinesia, rigidity, tremor, and hypokinetic speech. We defined cerebellar dysfunction as the presence of at least two signs, limb or gait ataxia along with ocular dysmetria and ataxic dysarthria. We defined autonomic failure by the presence of postural hypotension, sexual impotence (in males), or urinary incontinence without outflow obstruction or disorders of bladder suspension. The criteria for postural hypotension included an orthostatic drop of 30 mm Hg or more in systolic blood pressure and 20 mm Hg or more in diastolic blood pressure with an increase in heart rate of no more than 10 beats/min [37]. Blood pressure and pulse were measured with the patient supine and again 2 minutes after the patient assumed a standing position. None of the patients were taking medications that induce postural hypotension.

Eight patients with sOPCA were studied. The diagnosis of sOPCA was based on a history of sporadically occurring progressive deterioration of cerebellar function manifested by at least two signs, limb or gait ataxia along with ocular dysmetria and ataxia dystarthria, in the absence of other disorders such as sensory loss adequate to cause ataxia, medications, toxins, evidence of a neoplasm in the cerebellum or elsewhere, or evidence of multiple sclerosis or other diseases that can cause progressive cerebellar ataxia. A careful family history was taken to ensure that the disorder was sporadic. The diagnosis was assisted by finding cerebellar and brainstem atrophy in magnetic resonance images (MRIs) in all of the patients studied (see Table 1), but this was not essential because OPCA can occur without demonstrable atrophy in anatomical imaging studies [38]. Three women with sOPCA (Patients 9, 10, and 12) had mild degrees of urinary incontinence, but this was attributed to peripheral bladder mechanisms and not to autonomic involvement.

The patients were evaluated with a complete history, physical examination, neurological examination, laboratory tests to exclude other diseases, and MRI to exclude demyelinating disease and structural abnormalities. Speech was evaluated as described previously [39]. Laboratory tests included a com-
Table 1. Clinical Features of the Patients with Multiple System Atrophy (MSA) and Sporadic Olivopontocerebellar Atrophy (sOPCA)*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Medications</th>
<th>Duration of symptoms (yr)</th>
<th>Akinesia</th>
<th>Rigidity</th>
<th>Tremor at rest</th>
<th>Hypokineti c speech</th>
<th>Ocular dysmetria</th>
<th>Gait ataxia</th>
<th>Limb ataxia</th>
<th>Ataxic speech</th>
<th>Spastic speech</th>
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<th>Postural hypotension</th>
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<th>MRI findings</th>
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<tr>
<td>1</td>
<td>F</td>
<td>69</td>
<td>MSA</td>
<td>Fluoxetine, 20 mg; amitriptyline, 50 mg</td>
<td>4</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>-</td>
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<td>2</td>
<td>M</td>
<td>67</td>
<td>MSA</td>
<td>Amitriptyline, 30 mg; baclofen, 30 mg</td>
<td>10</td>
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<td>+</td>
<td>-</td>
<td>+</td>
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<td>+</td>
<td>-</td>
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<td>3</td>
<td>M</td>
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<td>MSA</td>
<td>Carbidopa/ levodopa, 125/500; Selegiline, 5 mg</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>++</td>
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</tr>
</tbody>
</table>

*Rating scale: = normal; + = mild; ++ = moderate; +++ = severe. Trace levels were rated as normal.

PET studies were conducted similarly for all subjects. A catheter was placed in a radial artery for blood sampling. Radioactive fiducial markers placed on the scalp were used to register the dynamic sequence of frames, correcting for any motion that occurred throughout the study. The subjects lay quietly on a table, with eyes open and ears unoccluded and alert but not speaking. The subjects were imaged with a Siemens ECAT EXACT-47 PET scanner, which has an intrinsic in-plane resolution of 6.0-mm full width at half maximum (FWHM) at the center of the field of view and an axial resolution of 5.0-mm FWHM. The reconstructed resolution is approximately 9.0-mm FWHM. Forty-seven planes with a 3.375-mm center-to-center separation were imaged simultaneously. Attenuation correction was calculated by the standard ellipse method.

Anatomically configured volumes of interest (VOIs) were identified in summed activity maps from 0 to 7.5 minutes after injection. VOIs were placed in identical areas on all frames of the realigned dynamic sequence of scans for the caudate nucleus, putamen, thalamus, cerebellar hemispheres, and frontal cortex. VOIs were acquired from three adjacent axial levels that best represented these structures. Data from the frontal cortex were used to normalize the data taken from cerebral blood flow. Serum profiles of hepatic and renal function; brainstem auditory, visual, and somatosensory evoked potentials; serum levels of vitamins E and B12 and folic acid, and studies of thyroid function. In patients with symptoms for less than 3 years, a search was made for an occult malignancy, including breast and pelvic examinations in women, prostate examination in men, acid phosphatase and prostate-specific antigen measurements, stool guaiac tests for occult blood, and chest x-ray studies. In addition, anti-Purkinje cell antibodies were sought in blood samples from patients with ataxia of less than 3 years duration. All patients were evaluated with MRI to determine the extent of volume loss of the structures under study. The extent of volume loss was evaluated from the scans and is listed in Table 1. The neurological examinations were conducted by a neurologist (S.G.) blinded to the PET data.

Positron Emission Tomography Studies

DTBZ in racemic form was synthesized by [14C]methylation of 9-O-desmethylhydroxytetrabenazine. We administered by intravenous bolus 18 ± 1 mCi containing less than 50 µg of mass of DTBZ and collected arterial blood samples and a sequence of 15 scans over the following 60 minutes [35].
Pharmacokinetic Analysis

The VOI data were fitted to a three-compartment tracer kinetic model using standard nonlinear least-squares parameter estimation. Kinetic rate constants \( K_t \) to \( k_i \) and cerebral blood volume were fitted parameters. Analysis resulted in regional estimates of ligand transport from plasma to brain \( (K_t) \), which is highly correlated with flow since the single-pass extraction fraction is approximately 50%, and total tissue distribution volume \( (DV) \) of DTBZ relative to plasma \( (DV = (K_t/k_j)(1 + k_j/k_i)) \) [40].

Data Analysis

Determinations of DTBZ \( K_t \) and \( DV \) in individual structures were normalized to values from the frontal cortex, which contains very little VMAT2 and is relatively spared in the diseases under study. The regional total DV data were converted to specific DV by computing the following: \( \text{Regional} \ DV - \frac{\text{Frontal} \ DV}{\text{Frontal} \ DV} \). Differences in specific binding between groups were tested with analysis of covariance (ANCOVA) adjusting for age, as explained below. A separate single-factor ANCOVA was tested for each of the four regions. For regions demonstrating a significant overall group difference, specific comparisons with two group \( t \) tests were performed between groups. Significance levels for individual comparisons were not corrected for multiple comparisons, and no corrections were made for the effects of tissue atrophy.

Age Effects

In a concurrent investigation utilizing racemic DTBZ, we found a significant decline of striatal DV values with increasing age in a sampling of normal control subjects with a broader age range [35]. Accordingly, we utilized ANCOVA to adjust for age in our analysis, even though, in the subset studied, more limited ranges in age were included, and age was not significantly associated with the values of \( K_t \) or specific binding in regions in which they distinguished the groups \( (p > 0.05 \text{ in all cases}) \). The adjustment for age had only minor effects on the results.

Results

\([1]C\)Dihydroterabenazine Specific Binding

ANCOVA revealed significant differences between groups in the caudate nucleus \( (F_{2,7} = 7.2, p = 0.005) \) and putamen \( (F_{2,7} = 4.9, p = 0.02) \) but not in the thalamus or cerebellum \( (p > 0.20) \). Adjusted means in the caudate nucleus and putamen were ordered as follows: MSA < sOPCA < control (Table 2, Figs 1, 2). Specifically, in the MSA group, the adjusted mean values for the caudate nucleus and putamen were significantly decreased in comparison to those for both normal control subjects and sOPCA patients. The magnitude of the decreases in specific binding below normal values in the MSA subjects averaged 61% in the caudate nucleus \( (p = 0.002) \) and 58% in the putamen \( (p = 0.009) \). Individual specific binding values in the caudate nucleus were reduced by more than 3 standard deviations below the normal control mean in 3 of the 4 MSA subjects. Specific binding in the putamen was reduced by more than 2.5 standard deviations in each of the same 3 patients. The fourth MSA patient, corresponding to the uppermost point in each of the four regions plotted in Figure 2, had relatively low specific binding values in the frontal cortex, and thus the data for this patient appear less decreased after normalization than before. For this patient, normalization of the values in the caudate nucleus and putamen to a different brain region such as the thalamus resulted in striatal decreases that were nearly equivalent to those of the other 3 MSA patients. Independent evaluation of the MRIs of all 4 MSA patients by two of us (S. G., K. A. F.) blinded to the PET data revealed no greater evidence of frontal cortical atrophy in this patient than the other 3. Thus, the findings in this patient do not appear to result from the effects of partial volume averaging owing to tissue atrophy.

In the sOPCA group the mean decrease of specific binding in comparison to the normal control values was not as great as in MSA, averaging 26% for the caudate nucleus \( (p = 0.05) \) and 24% for the putamen \( (p = 0.11) \) (see Table 2). Individual striatal specific binding values in sOPCA patients were more variable than those in MSA, with values for only 2 of 8 patients falling lower than 2 standard deviations below the control group mean for the caudate nucleus, and values for only 1 of 8 for the putamen.

\([1]C\)Dihydroterabenazine Transport \( (K_t) \)

Analysis of variance revealed significant differences between groups only in the cerebellum \( (F_{2,1} = 6.4, p = 0.008) \), where the means were in the following order: sOPCA < MSA < control. Subsequent pair-wise testing revealed that the only significant difference in cerebellar \( K_t \) between groups was a decrease in the sOPCA group as compared with the normal control group (Table 3). Although the MSA group showed no significant

\[ \text{Table 2. \([1]C\)Dihydroterabenazine Specific Binding} \]

<table>
<thead>
<tr>
<th>Group</th>
<th>Caudate Nucleus</th>
<th>Putamen</th>
<th>Thalamus</th>
<th>Cerebellum</th>
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<tbody>
<tr>
<td>Control</td>
<td>0.79 ± 0.16</td>
<td>0.78 ± 0.22</td>
<td>0.06 ± 0.05</td>
<td>−0.04 ± 0.12</td>
</tr>
<tr>
<td>sOPCA</td>
<td>0.58 ± 0.23</td>
<td>0.60 ± 0.25</td>
<td>0.03 ± 0.06</td>
<td>−0.09 ± 0.09</td>
</tr>
<tr>
<td>MSA</td>
<td>0.30 ± 0.16</td>
<td>0.33 ± 0.21</td>
<td>0.05 ± 0.16</td>
<td>−0.17 ± 0.17</td>
</tr>
</tbody>
</table>

Values represent the mean ± standard deviation. Means are age adjusted by analysis of covariance.

1Significantly different from normal control value, \( p = 0.05 \).
2Significantly different from normal control value, \( p = 0.002 \).
3Significantly different from normal control value, \( p = 0.009 \).
sOPCA = sporadic olivopontocerebellar atrophy; MSA = multiple system atrophy.
Fig 1. Distribution volume of $[^{11}C]$dihydrotetrabenazine ([C-11]DTBZ DV) in the basal ganglia (upper row) and cerebellum (lower row) of a 69-year-old male normal control subject, compared to a 60-year-old woman with sporadic olivopontocerebellar atrophy (sOPCA) and a 63-year-old man with multiple system atrophy (MSA).

differences from control values, cerebellar $K_1$ values for 2 of the 4 MSA patients were decreased to levels as low as the sOPCA values, but values for the other 2 were within the range of the normal control values. The 2 MSA patients with low cerebellar $K_1$ values had clinical signs of cerebellar dysfunction in addition to extrapyramidal and autonomic disturbances, whereas the other 2 patients had only extrapyramidal and autonomic signs.

**Discussion**

Many previous studies showed evidence of both striatal degeneration and decreased density of striatal monoaminergic presynaptic terminals in MSA. Investigations utilizing $[^{18}F]$fluorodeoxyglucose (FDG) to examine local cerebral metabolic rates for glucose revealed hypometabolism in the striatum [41-44] and also in the cerebral cortex [42, 44, 45], cerebellum [44-46], thalamus [44], and brainstem [44]. PET studies with $[^{18}F]$fluorodopa in MSA patients revealed diminished striatal uptake, suggesting that nigrostriatal dopaminergic terminals are damaged [47-49].

![Fig 2. Specific binding of $[^{11}C]$dihydrotetrabenazine normalized to the frontal cortex (FCx) in the caudate nucleus, putamen, thalamus, and cerebellum of individual normal control subjects (filled triangles) compared to patients with sporadic olivopontocerebellar atrophy (sOPCA, open circles) and patients with multiple system atrophy (MSA, filled circles). The horizontal bars indicate ±2 standard deviations about the normal control group mean.](image)
The results of the present study, which should be treated as suggestive rather than definitive given the small sample sizes, provide evidence of reduced density of monoaminergic terminals in some sOPCA patients, and give encouraging information concerning the utility of DTBZ in detecting striatal disease by measuring the density of monoaminergic presynaptic terminals. Utilizing only 4 patients with MSA and 8 with sOPCA compared with 9 normal control subjects, the study demonstrated significantly reduced DV in the caudate nucleus of both groups and in the putamen of the MSA group. Ligand K, did not differ between groups, suggesting that the differences in specific binding in the striatum likely do not result from the effects of tissue atrophy. The reductions of DTBZ DV in the striatum were greater in the MSA than the sOPCA group. The sOPCA group had a wide range of specific binding in the striatum, suggesting varying degrees of striatal dysfunction within this group. In contrast, all 4 MSA patients had deficits of striatal DTBZ specific binding, and all had correspondingly severe disturbances of extrapyramidal function associated with autonomic failure. The weaker evidence of decreased DTBZ specific binding in the sOPCA group suggests that at least some of the sOPCA patients had decreased nigrostriatal dopaminergic presynaptic terminals, which is in keeping with the clinical findings of trace levels of rigidity in Patients 7, 9, 11, and 12 and minimally detectable evidence of hypokinetic speech in Patients 5, 6, 7, 9, 10, and 12. Perhaps the sOPCA patients with reduced DTBZ specific binding will proceed over time to develop extrapyramidal symptoms as well as the autonomic symptoms and signs characteristic of MSA.

Even though the MSA patients on average had greater reductions of striatal DTBZ specific binding than did the sOPCA patients, several of the latter had decreased levels, some of which were reduced to the range observed in the MSA patients. As mentioned earlier, in a previous study [49], [18F]fluorodopa was used to investigate dopaminergic presynaptic terminals in patients with the “olivopontocerebellar atrophy form of multiple system atrophy” who probably are similar to the patients with sOPCA in the present study. Review of the data in that study reveals that most of the patients who had decreased [18F]fluorodopa binding showed no signs of extrapyramidal disorder on clinical examination. The results in that study may have been affected by compensatory upregulation of dopa decarboxylase activity and thus may have underestimated the decrease of nigrostriatal terminals in sOPCA. For a ligand to be helpful, it should be sensitive to differentiating disease from normal, which requires a favorable signal-to-noise ratio, and it should be accurate in estimating the severity of disease, which requires absence of bias. Upregulation decreases the “signal” (i.e., the
difference between the disease state and normal) and probably decreases the sensitivity of the fluorodopa method for detecting loss of nigrostriatal terminals. Moreover, upregulation introduces bias, leading to inaccurate results.

In the present study, the finding of similar levels of decline of DTBZ DV in some of the patients with sOPCA as compared with the MSA group raises the issue of why at least a few of these sOPCA patients did not show clinical signs of extrapyramidal dysfunction. One possible explanation is that the changes in sOPCA were greater in the caudate nucleus than the putamen, whereas it seems likely that abnormal function of the putamen is more strongly related to clinical signs of extrapyramidal dysfunction. Another possibility is that other sites of neural degeneration in the extrapyramidal motor system could mask the clinical expression of extrapyramidal disorder. These may include striatal neurons, but could also involve neurons in the subthalamus and globus pallidus.

All sOPCA patients in this study had clinical evidence of cerebellar dysfunction without symptoms or signs of extrapyramidal disease and without autonomic disorders. The consistent involvement of the cerebellum in these patients accounts for the significant decrease of K_i in the sOPCA group as compared with both the MSA and normal control groups. Only 2 of the 4 MSA patients showed clinical signs of cerebellar dysfunction, indicating that these patients probably had degenerative changes in the cerebellum. The other 2 MSA patients probably had mild or no degenerative changes in the cerebellum, and this may explain the lack of significant K_i effects observed in the cerebellum of the MSA patients as a group.

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