Cholinergic imaging in corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia

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Corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia are all part of a disease spectrum that includes common cognitive impairment and movement disorders. The aim of this study was to characterize brain cholinergic deficits in these disorders. We measured brain acetylcholinesterase activity by \[^{11}\text{C}\] N-methylpiperidin-4-yl acetate and positron emission tomography in seven patients with corticobasal syndrome (67.6 ± 5.9 years), 12 with progressive supranuclear palsy (68.5 ± 4.1 years), eight with frontotemporal dementia (59.8 ± 6.9 years) and 16 healthy controls (61.2 ± 8.5 years). Two-tissue compartment three-parameter model and non-linear least squares analysis with arterial input function were performed. \(k_3\) value, an index of acetylcholinesterase activity, was calculated voxel-by-voxel in the brain of each subject. The \(k_3\) images in each disease group were compared with the control group by using Statistical Parametric Mapping 2. Volume of interest analysis was performed on spatially normalized \(k_3\) images. The corticobasal syndrome group showed decreased acetylcholinesterase activity (\(k_3\) values) in the paracentral region, frontal, parietal and occipital cortices (P < 0.05, cluster corrected). The group with progressive supranuclear palsy had reduced acetylcholinesterase activity in the paracentral region and thalamus (P < 0.05, cluster corrected). The frontotemporal dementia group showed no significant differences in acetylcholinesterase activity. Volume of interest analysis showed mean cortical acetylcholinesterase activity to be reduced by 17.5% in corticobasal syndrome (P < 0.001), 9.4% in progressive supranuclear palsy (P < 0.05) and 4.4% in frontotemporal dementia (non-significant), when compared with the control group. Thalamic acetylcholinesterase activity was reduced by 6.4% in corticobasal syndrome.
(non-significant), 24.0% in progressive supranuclear palsy (P < 0.03) and increased by 3.3% in frontotemporal dementia (non-significant). Both corticobasal syndrome and progressive supranuclear palsy showed brain cholinergic deficits, but their distribution differed somewhat. Significant brain cholinergic deficits were not seen in frontotemporal dementia, which may explain the unresponsiveness of this condition to cholinergic modulation therapy.

Keywords: corticobasal syndrome; progressive supranuclear palsy; frontotemporal dementia; acetylcholinesterase; positron emission tomography

Abbreviations: MMSE = Mini-Mental State Examination; MP4A = N-methylpiperidin-4-yl acetate; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction

It has become increasingly clear that there is a considerable overlap among corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia. Corticobasal syndrome and progressive supranuclear palsy share several clinical features such as akineto–rigid syndrome, lack of balance, falls and eye movement abnormalities (Rinne et al., 1994). Non-fluent aphasia, apathy and executive dysfunction may be seen in corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia (Kertesz et al., 2003; Sha et al., 2006). The clinical overlap between corticobasal syndrome and progressive supranuclear palsy parallels the neuropathological overlap in these disorders (Rinne et al., 1994; Litvan et al., 1997; Schneider et al., 1997; Bergeron et al., 1998; Kertesz et al., 2000). The similarities in clinical manifestations and pathological features for these neurodegenerative disorders are of interest, since they may share common underlying molecular pathomechanisms, one of which is biochemical alterations in the tau protein (Houlden et al., 2001; Ingelsson et al., 2007). Corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia are progressive relentless diseases with few therapeutic options. Therefore, it is important to clarify their underlying neurochemical pathologies in order to further the understanding of their pathophysiology, which may lead to some clues for effective pharmacological intervention.

There have been a few in vivo studies of cholinergic systems in progressive supranuclear palsy (Asahina et al., 1998; Shinotoh et al., 1999), but no in vivo studies of cholinergic systems in corticobasal syndrome and frontotemporal dementia. The aim of this study is to characterize the cholinergic deficits in vivo in patients with clinically diagnosed corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia. N-methylpiperidin-4-yl acetate (MP4A) is an acetylcholine analogue, and PET with $^{11}$C]MP4A as a radiotracer allows us to measure brain acetylcholinesterase activity quantitatively in vivo (Irie et al., 1994; Iyo et al., 1997). Acetylcholinesterase is membrane-bound predominantly on presynaptic cholinergic neurons and, to a lesser degree, on postsynaptic cholinceptive neurons in the cerebral cortex. Therefore, by measuring cortical acetylcholinesterase activity, we can assess the integrity of the ascending cholinergic system from the nucleus basalis of Meynert. In the brainstem, there are two cholinergic nuclei, pedunculopontine and laterodorsal tegmental nuclei, which send ascending cholinergic fibres mainly to the thalamus (Mesulam et al., 1983). Thalamic acetylcholinesterase activity is thought to reflect the function of the ascending cholinergic systems from the pedunculopontine and laterodorsal tegmental nuclei. In the present study, we assessed the integrity of two major ascending cholinergic systems in patients with corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia by $^{[11]}$C]MP4A positron emission tomography.

Materials and methods

Subjects

Diagnosis of corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia was based on established consensus criteria (corticobasal syndrome: Boeve et al., 2003), probable progressive supranuclear palsy: National Institute of Neurological Diseases and Stroke—the Society for progressive supranuclear palsy criteria (Litvan et al., 1996), frontotemporal dementia: Lund–Manchester criteria (Neary et al., 1998). Briefly, the clinical diagnosis of corticobasal syndrome was based on the presence of progressive asymmetric rigidity and ideomotor apraxia, as well as other findings that reflect cortical (e.g. alien limb phenomenon, cortical sensory loss, myoclonus) and extrapyramidal (e.g. bradykinesia, tremor, dystonia) dysfunction. Probable progressive supranuclear palsy was defined by gradual progressive asymmetrical rigidity and bradykinesia, vertical gaze palsy and falls in the first year of disease onset. The diagnosis of frontotemporal dementia was based on (i) changes in personality and social behaviour, specifically apathy; (ii) dysexecutive features, specifically poor planning, forethought, reasoning or organization; and (iii) disorders of language and communication. None of the patients had a pathology-proven diagnosis in the present study.

Patients were recruited from the Department of Neurology, Chiba University Hospital, Chiba, Japan. Seven patients with corticobasal syndrome, 12 with progressive supranuclear palsy, eight with frontotemporal dementia and 16 age-matched healthy controls were enrolled, after exclusion of two patients with corticobasal syndrome (poor PET imaging quality) and one control subject (poor arterial input). None of the subjects had a history of taking anticholinergic, acetylcholinesterase inhibitor medication, or substance abuse. None of the subjects had cerebrovascular disease, past history of head trauma or encephalitis. Medications were discontinued more than 12 h before performing the PET scans. Mini-Mental State Examination (MMSE) was administered to all subjects. Parkinsonism was rated with Unified Parkinson’s Disease Rating Scale (UPDRS) motor score in patients with progressive supranuclear palsy.
This study was approved by the Institutional Review Board of the National Institute of Radiological Sciences. Written consent was obtained from all participants and their family members.

**Positron emission tomography**

After 10 min of transmission scan, emission data were acquired with a dynamic sequence of 16 PET scans over a 40 min period, using an EXACT47 scanner (Siemens/CTI, Knoxville, TN) with eyes covered and head immobilized. \[^{11}C\]MP4A (18.9 ± 2.8 mCi in 5 ml) was injected intravenously for 60 s using an infusion pump. Twenty-seven timed arterial blood samples were drawn from the radial artery. All emission scans were reconstructed by Hanning filter with a cut-off frequency of one-half of the maximum. After reconstruction, spatial resolution was 9 × 9 × 6 mm full-width at half maximum. Metabolite-corrected arterial plasma input function was obtained by fitting an exponential function to the plasma \[^{11}C\]MP4A radioactivity as described previously (Iyo et al., 1997; Shinotoh et al., 1999).

**Data analysis**

Image preprocessing was performed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 7.1 (Mathworks, Sherborn, MA). Each frame was realigned and individual mean images were created. In the corticobasal syndrome group, images were right-left flipped when the predominant side of clinical symptoms was on the left, so that the predominantly affected hemisphere was on the left side. \[^{11}C\]MP4A template image was created by using PET images and T1-weighted MRI in 11 healthy controls according to standard methods (Meyer et al., 1999). Each realigned image was individually normalized to the \[^{11}C\]MP4A template image by using the mean image as a target. These images were finally smoothed with a 12 mm full-width at half maximum Gaussian kernel filter.

Custom software operating with the IDL image analysis software (Research Systems Inc., Boulder, CO) was employed to calculate the kinetic parameters in each voxel, and subsequently to generate individual parametric images. Kinetic parameters, \( K_1 \) (mL/min/g) (tracer transport into tissue), \( k_2 \) (min\(^{-1}\)) (tissue clearance of authentic tracer back to blood) and \( k_3 \) (min\(^{-1}\)) (hydrolysis rate from \[^{11}C\]MP4A to N-[\(^{11}C\)] methylpipеридинol, i.e. acetylcholinesterase activity) were estimated in a two-tissue three-parameter model by fitting brain theoretical curves to observed brain PET data, using an unconstrained non-linear least-squares method and weighted time-activity curve as described elsewhere (Iyo et al., 1997; Shinotoh et al., 1999).

Volumes of interest were placed on normalized parametric images by using the WFU Pickatlas (Maldjian et al., 2003). The \( k_3 \) values were analysed in cerebral cortex and thalamus but not in cerebellum and striatum. Acetylcholinesterase activity in cerebral cortex and striatum is much higher than in cerebral cortex and thalamus. As a consequence, estimates of \( k_3 \) values in cerebral cortex and striatum are highly variable, and therefore not reliable, because of the flow-limitation effect of this technique (Nambo et al., 1999). Mean cortical \( k_3 \) value was calculated by averaging those in all Brodmann’s areas, in each subject. The brain was left-right flipped in patients with corticobasal syndrome, when the more affected side was the left side of the body. Therefore, the left brain was the more affected side in all patients with corticobasal syndrome in the following analysis. Asymmetry index of \( K_1 \) and \( k_3 \) values for each participant was calculated as follows:

\[
\text{Asymmetry index} = \frac{\text{Left cortex} - \text{Right cortex}}{\text{Left cortex} + \text{Right cortex}} \times 200.
\]

**Statistical analysis**

All Statistical Parametric Mapping analyses were conducted without performing grand mean scaling (i.e. absolute value). For voxel-based whole brain analysis, we created an explicit cerebrum mask by using the Talairach Daemon template implemented into the WFU Pickatlas to increase power by excluding extracerebral white matter (Lancaster et al., 2000; Maldjian et al., 2003). Cerebellum and striatum were also excluded from the present analyses since, due to its ceiling effect, this technique does not allow for estimation in these brain areas. Comparisons between each disease group and healthy controls were performed with the unpaired t-test option. Clusters were accepted as significant if \( P \) values corrected for multiple comparisons were 0.05 or less on the cluster-level with extent threshold above 400 voxels in \( k_3 \) parametric analyses. The exploratory threshold for voxel-based analyses in \( K_1 \) parametric images was chosen (\( P < 0.001 \) uncorrected, >400 voxels), since reduced perfusion in corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia was previously reported (Miller et al., 1991; Markus et al., 1995; Okuda et al., 2000; Zhang et al., 2001; Hossain et al., 2003; Le Ber et al., 2006; McNeill et al., 2007). All reported coordinates were in Montreal Neurological Institute standard space.

Group comparisons in demographic variables and volume of interest analyses were performed by one-way ANOVA followed by Bonferroni correction, using Statistical Package for the Social Sciences software (SPSS version 11, SPSS Inc., Chicago, IL). Correlation analyses between cortical \( k_3 \) values and total MMSE scores were performed in each group by Spearman’s rank correlation test. Correlation analysis between thalamic \( k_3 \) values, UPDRS motor score and axial subscore of UPDRS motor score (items 27–31) was also performed in patients with progressive supranuclear palsy.

**Results**

**Patients**

Demographic values are shown in Table 1. Age \([F(3,39) = 4.37, P = 0.10, \text{one-way ANOVA}] \) and gender \((P = 0.79, \text{chi-square}) \) did not differ among disease and control groups (Table 1). MMSE scores differed among groups \([F(3,39) = 14.4, P < 0.001]\) and post hoc analysis showed reduction of MMSE scores in the corticobasal syndrome \((P < 0.005) \) and frontotemporal dementia groups compared with the control group \((P < 0.001) \) (Table 1). Four patients with corticobasal syndrome were affected more on the right side and three patients with corticobasal syndrome more on the left side. The clinical features in corticobasal syndrome were: limb akinesia/rigidity 6/7, axial rigidity 4/7, myoclonic tremor 3/7; alien limb 4/6; supranuclear gaze palsy 3/7; and cortical sensory loss 3/4. All subjects with progressive supranuclear palsy presented with both supranuclear palsy and axial rigidity. Three patients with corticobasal syndrome and 10 patients with progressive supranuclear palsy were unresponsive to levodopa, and the remaining patients were not exposed to dopaminergic medications before the present study. The frontotemporal dementia group included six patients with behavioural variants of frontotemporal dementia, one patient with frontotemporal dementia with motor neuron disease and one patient with semantic
Acetylcholinesterase activity in disease groups compared with healthy controls

First, we compared the parametric $k_3$ brain images of disease and control groups ($P < 0.05$, cluster-corrected). In corticobasal syndrome, there was a reduction of $k_3$ value in prefrontal, orbitofrontal, parietal and occipital cortices and the paracentral region compared with the control group (Fig. 1, Table 2). The most prominent reduction in $k_3$ value for corticobasal syndrome was observed in the precentral region (Brodmann’s area 4) of the predominantly affected hemisphere. In progressive supranuclear palsy, reduction of $k_3$ values was detected in paracentral region and thalamus compared with the control group (Fig. 2, Table 2). There was no cluster with reduced $k_3$ values in the frontotemporal dementia group compared with healthy control brains. There was no cluster with increased $k_3$ values in any of the disease groups compared with healthy controls.

Volume of interest analysis demonstrated a significant difference in mean cortical $k_3$ values among groups [$F(3,39) = 7.41$, $P < 0.001$, one-way ANOVA] (Fig. 3A). Post hoc Bonferroni analysis revealed that, when compared with the healthy control group, mean cortical $k_3$ values were reduced in both corticobasal syndrome ($P < 0.001$, $-17.5\%$ reduction) and progressive supranuclear palsy groups ($P < 0.05$, $-9.4\%$ reduction), whereas mean cortical $k_3$ values in frontotemporal dementia did not differ from the healthy control group ($P = 1.0$, $-4.4\%$ reduction).

Mean cortical $k_3$ values in corticobasal syndrome were reduced compared with the frontotemporal dementia group ($P < 0.04$). Thalamic $k_3$ values were also different among groups [$F(3,39) = 3.99$, $P < 0.02$, one-way ANOVA] (Fig. 3B). Post hoc Bonferroni analysis demonstrated that thalamic $k_3$ values were reduced in the progressive supranuclear palsy group compared with the healthy controls ($P < 0.03$, $-24.0\%$ reduction). Thalamic $k_3$ values in the corticobasal syndrome group...
(P = 1.0, −6.4% reduction) and frontotemporal dementia group (P = 1.0, 3.3% increase) did not differ from the control group. Comparison of disease groups in terms of thalamic $k_3$ values showed reduction in the progressive supranuclear palsy group compared with the frontotemporal dementia group (P < 0.04).

Correlation analysis between mean cortical $k_3$ values and MMSE total scores in each group revealed that there was a positive correlation only in the corticobasal syndrome group (Spearman’s rho = 0.8, P < 0.04), but not in the progressive supranuclear palsy or frontotemporal dementia group (P ≥ 0.60). Thalamic $k_3$ values were not correlated with UPDRS motor scores or their axial subscores in patients with progressive supranuclear palsy (P > 0.05).

**Changes in perfusion of corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia**

There was reduction in $K_1$ values in the corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia

<table>
<thead>
<tr>
<th>Regions</th>
<th>Brodmann’s area</th>
<th>Coordinates</th>
<th>P-value</th>
<th>Extent</th>
<th>Z$_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls $&gt;$ corticobasal syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left paracentral region</td>
<td>4, 6</td>
<td>−4 −34 62</td>
<td>&lt;0.001</td>
<td>1565</td>
<td>5.39</td>
</tr>
<tr>
<td>Bilateral superior frontal and orbitofrontal lobe</td>
<td>10, 11, 25</td>
<td>10 56 −24</td>
<td>&lt;0.001</td>
<td>4947</td>
<td>5.31</td>
</tr>
<tr>
<td>Left paracentral region, precuneus, occipital lobe</td>
<td>1−4, 6, 7, 17−21, 37, 40, 43</td>
<td>−14 −96 18</td>
<td>&lt;0.001</td>
<td>12,148</td>
<td>5.26</td>
</tr>
<tr>
<td>Right parietal lobe</td>
<td>7, 39</td>
<td>26 −60 32</td>
<td>&lt;0.05</td>
<td>452</td>
<td>4.8</td>
</tr>
<tr>
<td>Right parietal lobe</td>
<td>7</td>
<td>26 −48 52</td>
<td>&lt;0.04</td>
<td>486</td>
<td>4.6</td>
</tr>
<tr>
<td>Right supplementary motor area</td>
<td>4, 6</td>
<td>36 −12 52</td>
<td>&lt;0.002</td>
<td>1054</td>
<td>4.21</td>
</tr>
<tr>
<td>Right inferior occipital lobe</td>
<td>18</td>
<td>32 −86 −18</td>
<td>&lt;0.02</td>
<td>659</td>
<td>4.15</td>
</tr>
<tr>
<td>Controls $&gt;$ progressive supranuclear palsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right precentral region</td>
<td>4, 6</td>
<td>28 −2 60</td>
<td>&lt;0.001</td>
<td>3020</td>
<td>4.72</td>
</tr>
<tr>
<td>Left paracentral region, insula, temporal lobe</td>
<td>1−4, 6, 13, 20, 21, 43, 44</td>
<td>−56 −2 22</td>
<td>&lt;0.001</td>
<td>3465</td>
<td>4.62</td>
</tr>
<tr>
<td>Left postcentral region, parietal lobe</td>
<td>1−5</td>
<td>−14 −36 68</td>
<td>&lt;0.001</td>
<td>4714</td>
<td>4.49</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>–</td>
<td>−16 −28 0</td>
<td>&lt;0.003</td>
<td>514</td>
<td>4.38</td>
</tr>
</tbody>
</table>

SPM, P-values corrected at the cluster level.

*P < 0.05 family-wise error corrected.
groups compared with the control group (Fig. 4, \( P < 0.001 \), voxel-uncorrected, extent threshold > 400). In corticobasal syndrome, there was asymmetric reduction of \( K_1 \) values, with more reduction on the predominantly affected side of the brain than the less affected side, in paracentral and parietal region. The progressive supranuclear palsy group showed reduction of \( K_1 \) values in frontotemporal cortices and thalamus. There was reduction of \( K_1 \) values in the mesial frontal and right temporal region in the frontotemporal dementia group. Detailed results of coordinates and \( Z \)-values are presented in the online Supplementary material.

Figure 4  Statistical parametric Z-score map showing reduction of \( K_1 \) values in the brains of patients with corticobasal syndrome (CBS), progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) compared with healthy control brains at the threshold of \( P < 0.001 \), uncorrected, extent threshold > 400 voxels. Left figure is rendered onto structural brain template. Right figure is superimposed on brain MRI with different section (red–yellow).
Laterality of $K_1$ and $k_3$ changes

The $K_1$ and $k_3$ values in each volume of interest are shown in Table 3. There was reduction of $k_3$ values in bilateral frontal, temporal, parietal and occipital cortices in the corticobasal syndrome group, while there was reduction of $K_1$ values only in the more affected brain hemispheres in the corticobasal syndrome group. Asymmetry index for $K_1$ and $k_3$ values in cerebral cortex and thalamus was calculated and compared between groups (Table 3). Asymmetry index for cortical $k_3$ tended to be high in the corticobasal syndrome group, but there was no main effect for cortical $k_3$ values $[F(3,39) = 1.31, P = 0.29]$ or thalamic $k_3$ value $[F(3,39) = 1.48, P = 0.23]$. No significant left/right differences were found in cortical and thalamic acetylcholinesterase activity in any of the disease groups, including the corticobasal syndrome group.

There was a main effect for cortical $K_1$ values $[F(3,39) = 4.79, P < 0.007]$. Post hoc Bonferroni test showed a difference in asymmetric index of cortical $K_1$ values between corticobasal syndrome and frontotemporal dementia ($P < 0.004$) and a trend towards difference between corticobasal syndrome and control group ($P = 0.10$). There was no main effect for thalamic $K_1$ value $[F(3,39) = 2.75, P = 0.06]$. A trend of difference in thalamic $K_1$ value was found between the controls and corticobasal syndrome group ($P = 0.06$), decreased in the affected side of corticobasal syndrome group.

Table 3 Acetylcholinesterase activity ($k_3$) and perfusion ($K_1$) value in volume of interest analysis$^a$ and asymmetry index$^b$

<table>
<thead>
<tr>
<th>Volume of Interest</th>
<th>Control ($k_3$)</th>
<th>Corticobasal syndrome ($k_3$)</th>
<th>Progressive supranuclear palsy ($k_3$)</th>
<th>Frontotemporal dementia ($k_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frontal, right</td>
<td>0.082 (0.001)</td>
<td>0.069 (0.005), $-15.8% ^c$</td>
<td>0.074 (0.002), $-9.7% ^c$</td>
</tr>
<tr>
<td></td>
<td>Frontal, left</td>
<td>0.081 (0.001)</td>
<td>0.067 (0.006), $-17.6% ^c$</td>
<td>0.074 (0.002), $-8.6%$</td>
</tr>
<tr>
<td></td>
<td>Temporal, right</td>
<td>0.076 (0.002)</td>
<td>0.065 (0.005), $-15.2% ^c, d$</td>
<td>0.070 (0.001), $-8.0%$</td>
</tr>
<tr>
<td></td>
<td>Temporal, left</td>
<td>0.078 (0.001)</td>
<td>0.062 (0.006), $-21.1% ^c, d$</td>
<td>0.071 (0.002), $-9.0%$</td>
</tr>
<tr>
<td></td>
<td>Parietal, right</td>
<td>0.072 (0.001)</td>
<td>0.061 (0.005), $-18.5% ^c$</td>
<td>0.066 (0.001), $-8.2%$</td>
</tr>
<tr>
<td></td>
<td>Parietal, left</td>
<td>0.073 (0.001)</td>
<td>0.059 (0.006), $-18.8% ^c, d$</td>
<td>0.067 (0.001), $-8.7%$</td>
</tr>
<tr>
<td></td>
<td>Occipital, right</td>
<td>0.064 (0.001)</td>
<td>0.053 (0.003), $-16.8% ^c, d$</td>
<td>0.058 (0.002), $-9.0%$</td>
</tr>
<tr>
<td></td>
<td>Occipital, left</td>
<td>0.067 (0.001)</td>
<td>0.054 (0.004), $-18.9% ^c, d$</td>
<td>0.061 (0.002), $-9.0%$</td>
</tr>
<tr>
<td></td>
<td>Thalamus, right</td>
<td>0.170 (0.008)</td>
<td>0.165 (0.015), $-3.1%$</td>
<td>0.134 (0.006), $-21.3% ^d$</td>
</tr>
<tr>
<td></td>
<td>Thalamus, left</td>
<td>0.184 (0.011)</td>
<td>0.167 (0.019), $-9.1%$</td>
<td>0.135 (0.005), $-26.4% ^c$</td>
</tr>
<tr>
<td></td>
<td>Cortex AI</td>
<td>1.14 (0.57)</td>
<td>$-3.2$ (1.84)</td>
<td>1.33 (1.94)</td>
</tr>
<tr>
<td></td>
<td>Thalamus AI</td>
<td>6.81 (4.66)</td>
<td>0.28 (5.17)</td>
<td>1.39 (3.62)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume of Interest</th>
<th>Control ($K_1$)</th>
<th>Corticobasal syndrome ($K_1$)</th>
<th>Progressive supranuclear palsy ($K_1$)</th>
<th>Frontotemporal dementia ($K_1$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frontal, right</td>
<td>0.396 (0.017)</td>
<td>0.324 (0.017), $-18.0%$</td>
<td>0.316 (0.018), $-20.0% ^c$</td>
</tr>
<tr>
<td></td>
<td>Frontal, left</td>
<td>0.394 (0.017)</td>
<td>0.303 (0.017), $-22.9% ^c$</td>
<td>0.313 (0.017), $-20.4% ^c$</td>
</tr>
<tr>
<td></td>
<td>Temporal, right</td>
<td>0.401 (0.017)</td>
<td>0.338 (0.020), $-15.7%$</td>
<td>0.339 (0.020), $-15.3%$</td>
</tr>
<tr>
<td></td>
<td>Temporal, left</td>
<td>0.409 (0.017)</td>
<td>0.310 (0.023), $-24.3% ^c$</td>
<td>0.341 (0.019), $-16.7%$</td>
</tr>
<tr>
<td></td>
<td>Parietal, right</td>
<td>0.413 (0.016)</td>
<td>0.332 (0.021), $-19.6%$</td>
<td>0.360 (0.019), $-12.6%$</td>
</tr>
<tr>
<td></td>
<td>Parietal, left</td>
<td>0.419 (0.017)</td>
<td>0.307 (0.021), $-26.8% ^c, d$</td>
<td>0.361 (0.017), $-13.9%$</td>
</tr>
<tr>
<td></td>
<td>Occipital, right</td>
<td>0.383 (0.015)</td>
<td>0.337 (0.017), $-12.1%$</td>
<td>0.328 (0.017), $-14.5%$</td>
</tr>
<tr>
<td></td>
<td>Occipital, left</td>
<td>0.398 (0.015)</td>
<td>0.332 (0.021), $-16.6%$</td>
<td>0.338 (0.017), $-15.2%$</td>
</tr>
<tr>
<td></td>
<td>Thalamus, right</td>
<td>0.483 (0.021)</td>
<td>0.398 (0.020), $-17.6%$</td>
<td>0.382 (0.002), $-21.1% ^c$</td>
</tr>
<tr>
<td></td>
<td>Thalamus, left</td>
<td>0.492 (0.020)</td>
<td>0.375 (0.021), $-23.9% ^c$</td>
<td>0.387 (0.021), $-21.3% ^c$</td>
</tr>
<tr>
<td></td>
<td>Cortex AI</td>
<td>1.01 (0.59)</td>
<td>$-6.78$ (2.41)$^d$</td>
<td>0.45 (0.70)</td>
</tr>
<tr>
<td></td>
<td>Thalamus AI</td>
<td>1.91 (1.46)</td>
<td>$-6.24$ (1.48)</td>
<td>1.33 (1.19)</td>
</tr>
</tbody>
</table>

$K_1$: ml/min/g, $k_3$: min$^{-1}$.

Asymmetry index (AI) = (left cortex−right cortex)/(left cortex + right cortex) × 200.

The brain is left-right flipped in corticobasal syndrome group, when the more affected side is the left side of the body.

a Mean (SEM), percent reduction relative to mean of healthy control group.
b Mean (SEM).
c Reduced compared to healthy controls ($P < 0.05$), one-way ANOVA, post hoc Bonferroni.
d Reduced compared to frontotemporal dementia ($P < 0.05$), one-way ANOVA, post hoc Bonferroni.

Discussion

To our knowledge, this is the first in vivo study of brain cholinergic function in patients with corticobasal syndrome and frontotemporal dementia. Cerebral cortical acetylcholinesterase activity was moderately reduced in corticobasal syndrome and mildly reduced in progressive supranuclear palsy, while thalamic acetylcholinesterase activity was remarkably reduced only in progressive supranuclear palsy. There was no acetylcholinesterase activity deficit in cerebral cortex and thalamus in the frontotemporal dementia group. Cortical acetylcholinesterase activity was correlated with general cognitive function measured by MMSE in the corticobasal syndrome group. There was a trend toward lateralizing asymmetry in cortical acetylcholinesterase reduction that was more severe in the more affected brain hemisphere and regionally more severe in the parieto-occipital and orbitofrontal region in the corticobasal syndrome group. Deficits in acetylcholinesterase activity in cerebral cortex were symmetrical in the progressive supranuclear palsy and frontotemporal dementia groups.

Pathological studies of post-mortem brains with corticobasal syndrome showed that the nucleus basalis of Meynert is relatively preserved and contains a few neurofibrillary tangles (Dickson, 1999; Dickson et al., 2002). While abnormal tau processing is limited to grey matter in Alzheimer’s disease, white matter is
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Our previous MP4A PET study using manual regions of interest in corticobasal syndrome (Forman et al., 2002). White matter change has been detected by structural MRI studies showing subcortical T2 high intensity in primary and supplementary motor cortices (Soliveri et al., 1999; Winkelmann et al., 1999) and a study of diffusion tensor tractography demonstrated reduction of corticospinal tract in corticobasal syndrome (Boelmans et al., 2009). Taken together, the reduction of cortical acetylcholinesterase activity in corticobasal syndrome could be explained by impairment of cholinergic fibres from the nucleus basalis of Meynert or dysfunction of cholinergic neurons without significant loss of cholinergic neurons in the nucleus basalis of Meynert.

Perfusion, an index of cortical neuronal activity, was asymmetrically reduced in cerebral cortex of the corticobasal syndrome group in the present study, which is in accord with previous PET studies showing asymmetric hyperperfusion or hypometabolism in the frontal, parietal, temporal cortices, basal ganglia and thalamus (Markus et al., 1995; Okuda et al., 1999, 2000; Brooks, 2000; Zhang et al., 2001; Hossain et al., 2003; Eckert et al., 2005). We found a correlation between MMSE scores and cortical acetylcholinesterase activity in the corticobasal syndrome group, suggesting that cognitive decline might be caused by cholinergic dysfunction in corticobasal syndrome. Cholinergic stimulant therapy may improve cognitive function of corticobasal syndrome patients.

Loss of cortical acetylcholinesterase activity was mild and loss of thalamic acetylcholinesterase activity was pronounced in progressive supranuclear palsy. These results are concordant with that of our previous [11C]MP4A PET study using manual regions of interest (Shinotoh et al., 1999). Post-mortem progressive supranuclear palsy brain studies showed that neuronal cell loss in the nucleus basalis of Meynert was variable, ranging from −12.6 to −73.8% less than those in Parkinson’s disease and Alzheimer’s disease (Tagliavini et al., 1984; Rogers et al., 1985; Ruberg et al., 1985). Neurochemical and histochemical studies of post-mortem brains showed that choline acetyltransferase activity is only mildly reduced in frontal cortex of progressive supranuclear palsy (Ruberg et al., 1985; Suzuki et al., 2002). The mild reduction of acetylcholinesterase activity in the progressive supranuclear palsy group in the present study is in agreement with those results from the post-mortem brain studies. In another PET study with 11C-N-methyl-4-piperidyl benzilate, we demonstrated that there was no significant change in total muscarinic acetylcholine receptors in cerebral cortex and thalamus in patients with progressive supranuclear palsy, suggesting that cholinocceptive neurons are not impaired in cerebral cortex or thalamus in progressive supranuclear palsy (Asahina et al., 1998). Neuropathological studies have demonstrated severe loss of pedunculopontine nucleus neurons in progressive supranuclear palsy (Hirsch et al., 1987; Zweig et al., 1987; Jellinger, 1988; Warren et al., 2005). Taken together, the pronounced reduction of thalamic acetylcholinesterase activity in patients with progressive supranuclear palsy is thought to reflect a loss of ascending cholinergic fibres from pedunculopontine and laterodorsal tegmental nuclei rather than impairment of cholinocceptive neurons in thalamus, although we did not find any significant correlation between thalamic k3 values and UPDRS motor scores or axial scores of UPDRS in the present study. The impairment of pedunculopontine nucleus can produce disturbances in gait, posture, eye movement and attention (Mendez et al., 1994), which are main clinical features in progressive supranuclear palsy.

Since cortical involvement in progressive supranuclear palsy is sparse, behavioural disturbances have previously been attributed to disconnection of the frontal cortex by prominent subcortical pathology (Agid et al., 1987; Litvan et al., 1996). Our results suggest that dysfunction of the thalamocortical pathway could also contribute to the neuropsychological impairment in progressive supranuclear palsy.

In the present study, there was a reduction in frontal cortex and thalamus perfusion in the progressive supranuclear palsy group, a result in accord with previous studies showing reduction of perfusion and glucose metabolism in prefrontal cortex, peri-insula, caudate nucleus, thalamus and mesencephalon (D’Antona et al., 1985; Salmon et al., 1997; Garraux et al., 1999; Hosaka et al., 2002; Van Laere et al., 2006; Eckert et al., 2008).

In spite of the mounting evidence of cholinergic impairment in the brain of patients with progressive supranuclear palsy, a number of drug trial studies have failed to show beneficial effects of cholinergic stimulant therapy (Foster et al., 1989; Litvan et al., 1989, 2001; Fabbriini et al., 2001). However, in the donepezil study, patients with progressive supranuclear palsy who did not receive dopaminergic therapy showed better memory scores on the category cued recall (Litvan et al., 2001). Additionally, a physostigmine trial in a small group of patients with progressive supranuclear palsy showed increased brain metabolism and some improvement in memory and visuospatial attention (Kertzman et al., 1990; Blin et al., 1995). On the contrary, brain cholinergic blockade by scopolamine significantly impairs cognitive and gait function in progressive supranuclear palsy by increased sensitivity (Litvan et al., 1994). The present study confirmed the brain cholinergic deficits in progressive supranuclear palsy. Other forms of acetylcholine modulating agent might be helpful for improving clinical symptoms in patients with progressive supranuclear palsy.

Accumulating neuropathological evidence has indicated that both cortical acetylcholinesterase and choline acetyltransferase are unaltered, even in the advanced stage of frontotemporal dementia (White et al., 1977; Yates et al., 1980; Wood et al., 1983; Meier-Ruge et al., 1984; Hansen et al., 1988; Sparks and Markesbery, 1991; Procter et al., 1999). A study of cerebrospinal fluid in frontotemporal dementia demonstrated a normal acetylcholinesterase level (Wallin et al., 2003). Our result in the frontotemporal dementia group agreed with this. A therapeutic trial of acetylcholinesterase inhibitor in frontotemporal dementia failed to show any efficacy (Mendez et al., 2007). Dementia and behavioural abnormalities in frontotemporal dementia are probably related to impairment of systems other than the cholinergic system. The present frontotemporal dementia group showed reduction of perfusion in the mesial frontal and left dorsolateral frontal regions. Previous perfusion single photon emission computed tomography studies have repeatedly shown frontal and...
anterior temporal reduction and relative preservation of parietal and occipital cortices (Miller et al., 1991; Le Ber et al., 2006; McNeill et al., 2007). Although the reduction of frontotemporal perfusion was modest in patients with frontotemporal dementia, our result is in agreement with those previous observations, supporting the diagnoses of patients with frontotemporal dementia in the present study. Patients with frontotemporal dementia had to be either calm or inert enough to stay still in the PET scanner bed for nearly an hour. Patients with frontotemporal dementia in this study were in the early stage of the disease (mean disease duration 2.6 years). This might have resulted in modest frontotemporal hypoperfusion compared with previous perfusion studies.

In contrast to the frontotemporal dementia group in this study, we previously observed profound reduction of acetylcholinesterase activity in cerebral cortex and thalamus in two patients with frontotemporal dementia and parkinsonism linked to chromosome-17 (FTDP-17) who had a mutation (N279K) in the microtubule-associated protein tau (MAPT) gene (Hirano et al., 2006). The pathologies and the clinical features of FTDP-17 with MAPT gene mutation mimic corticobasal syndrome (Bird et al., 1999; Nasreddine et al., 1999; Dickson et al., 2002). Interestingly, FTDP-17 with MAPT gene mutation is also characterized by four-repeat tau deposition along with corticobasal syndrome and progressive supranuclear palsy, while Pick’s disease is characterized predominantly by three-repeat tau deposition. Frontotemporal dementia with motor neuron disease and semantic dementia do not usually show tau pathology. Corticobasal syndrome and progressive supranuclear palsy are closer to FTDP-17 than frontotemporal dementia, including Pick’s disease (Boeve et al., 2003), which may explain the difference in the cholinergic pathology in these disorders.

We have studied brain acetylcholinesterase activity in other neurodegenerative diseases by PET and found that mean reduction of cortical acetylcholinesterase activity, compared with normal controls, was 13% in mild to moderate late-onset Alzheimer’s disease, 23% in mild to moderate early-onset Alzheimer’s disease, 12% in Parkinson’s disease without dementia, 27% in Parkinson’s disease with dementia and dementia with Levy bodies, 21 and 36% in two patients with N279K FTDP-17 and 6% in a cerebellar variant of multiple system atrophy (Shinotoh et al., 2000; Hirano et al., 2006, 2008; Shimada et al., 2009). Compared with the reduction of cortical acetylcholinesterase activities in these disorders, the reduction of cortical acetylcholinesterase was moderate in corticobasal syndrome and mild in progressive supranuclear palsy.

The limitation of the present study is the lack of pathological data from the patients. There is growing evidence that patients with clinically diagnosed corticobasal syndrome can have alternative pathologies including Alzheimer's disease, progressive supranuclear palsy and frontotemporal dementia (Boeve et al., 1999; Kertesz et al., 2000; Josephs et al., 2006; Sha et al., 2006). Nevertheless, as we included only patients with corticobasal syndrome who were diagnosed on the basis of movement disorder, and none of them had initial episodic memory impairment, the pathological diagnosis of corticobasal degeneration rather than Alzheimer’s disease was strongly suggested. Pathological diagnosis could overlap, but it is unlikely to have a cholinergic deficit in frontal syndromes when Parkinsonian features are absent.

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Supplementary material

Supplementary material is available at Brain online.

References


