Cholinergic correlates of cognitive impairment in Parkinson’s disease: comparisons with Alzheimer’s disease

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SUMMARY Dementia in Parkinson’s disease has previously been attributed to the presence in the cerebral cortex of Alzheimer-type neuropathological abnormalities. New evidence suggests, however, that dementia in this disease usually occurs in the absence of substantial Alzheimer-type changes in the cortex and may be related to abnormalities in the cortical cholinergic system. Thus, in Parkinsonian patients with dementia there were extensive reductions of choline acetyltransferase and less extensive reductions of acetylcholinesterase in all four cortical lobes. Choline acetyltransferase reductions in temporal neocortex correlated with the degree of mental impairment assessed by a test of memory and information but not with the extent of plaque or tangle formation. In Parkinson’s but not Alzheimer’s disease the decrease in neocortical (particularly temporal) choline acetyltransferase correlated with the number of neurons in the nucleus of Meynert suggesting that primary degeneration of these cholinergic neurons may be related, directly or indirectly, to declining cognitive function in Parkinson’s disease.

Evidence of an involvement of the transmitter, acetylcholine, in memory1 2 has stimulated investigation of the cholinergic system in disorders of the human brain affecting memory and other cognitive functions. An abnormality of the cholinergic system in Alzheimer-type dementia is now well established and correlations between the severity of the disease (assessed either neuropathologically or clinically) and reductions in the cortical cholinergic enzyme, choline acetyltransferase (CAT), have been reported.3 4 Dementia or cognitive impairment also occurs in a significant number of patients with Parkinson’s disease (for review, see reference 5) and several reports have attributed the dementia to the presence of Alzheimer-type cortical neuropathology in these cases.6 7

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The condition of the cortical cholinergic system in Parkinson’s disease is unclear since some groups have reported, in cases not assessed for mental function, normal CAT activities8 9 whereas another group has reported CAT reductions correlating with the degree of dementia assessed retrospectively.10 With respect to the condition of the principal cholinergic nucleus innervating the neocortex—the nucleus of Meynert—there is evidence that loss of neurons occurs in both Parkinson’s and Alzheimer’s disease.11 12 Whether this neuronal degeneration in both diseases is closely associated with the cortical cholinergic abnormalities (assessed biochemically) is unclear although this issue is relevant to the question of whether subcortical cholinergic abnormalities represent primary or secondary features of the disease processes.

The present investigation was undertaken primarily to examine the relationship between, on the one hand, cognitive impairment or dementia in Parkinson’s disease and, on the other hand, the presence of cortical cholinergic abnormalities, cortical
Alzheimer-type pathology and Meynert neuron loss. Comparisons with Alzheimer’s disease are included and show that although cortical cholinergic biochemical activities are almost identical in Parkinsonian and Alzheimer-type dementia, the neuropathological involvement of the neocortex and Meynert nucleus generally distinguishes between the two disorders. Thus, Parkinsonian intellectual deficit, but not Alzheimer-type dementia, is invariably accompanied by neuron loss in the nucleus of Meynert whereas the presence of neocortical neurofibrillary tangles and numerous senile plaques are virtually confined to Alzheimer’s disease. A preliminary report of some of these findings has been published.13

Subjects and methods

Cases
Case details are provided in table 1. Eight control cases, with no neurological or psychiatric symptoms (age range 63 to 89 yr), 14 cases with Parkinson’s disease (age range 62 to 80 yr) and eight cases of Alzheimer’s disease (age range 73 to 92 yr) were examined at necropsy between 5 and 48 hours post mortem. Amongst the Parkinsonian cases, cognitive impairment was present in 10. Recent mental test scores,14 available for seven, ranged from 0 to 27 out of a maximum possible score of 37. The remaining four Parkinsonian cases were not known to have had an established dementia syndrome during life. In two of the ten cognitively impaired Parkinsonian cases a dementia syndrome was a major feature in the initial psychiatric presentation. Extrapyramidal symptoms were not prominent in these two cases and the presentation, although not entirely typical of Alzheimer’s disease, included memory impairment, right left disorientation, agnosia, constructional apraxia, and nominal aphasia. However, subsequent neuropathological examination (see below) indicated a diagnosis of Parkinson’s rather than Alzheimer’s disease. The eight Alzheimer-type cases fulfilled clinical and pathological criteria previously described14–16 and, as judged by available test scores and cortical plaque densities, were generally moderate rather than severe cases.

Neuropathological Assessment
Following removal of samples for biochemical analyses (see below) the remaining left and intact right hemispheres were subjected to standard macro- and microscopic examination.15 16 In all 14 of the Parkinsonian cases, but neither the normal nor Alzheimer groups, both cell loss and Lewy body formation were evident in the dopaminergic cells of the substantia nigra. With respect to Alzheimer-type pathological changes in the cortex, neurofibrillary tangles were absent and the senile plaques were within the normal range13 (0 to 14 mean plaques per 1-3 mm²) for this age group in the normal cases and 11 of the 14 Parkinsonian cases. In the three

Table 1  Case details

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Normal</th>
<th>Parkinson’s disease</th>
<th>Combined Parkinson’s and Alzheimer’s disease</th>
<th>Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(a) Mentally normal</td>
<td>(b) Mentally impaired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)†</td>
<td>79 ± 8</td>
<td>74 ± 10</td>
<td>77 ± 7</td>
<td>77 ± 13</td>
</tr>
<tr>
<td>Gender (males: females)</td>
<td>4:4</td>
<td>1:3</td>
<td>0:3</td>
<td>2:6</td>
</tr>
<tr>
<td>Postmortem interval (h)†</td>
<td>26 ± 7</td>
<td>24 ± 17</td>
<td>25 ± 15</td>
<td>17 ± 8</td>
</tr>
<tr>
<td>Neocortical plaque count† (mean number/1-3 mm diameter field)</td>
<td>5-7 ± 4-0</td>
<td>7-6 ± 8-4</td>
<td>6-2 ± 7-1</td>
<td>34-0 ± 9-8</td>
</tr>
<tr>
<td>Neocortical neurofibrillary tangles</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Test scores*</td>
<td>—</td>
<td>18 ± 10 (5)</td>
<td>2, 13</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>Meynert nucleus neuron count† (mean cell number/20 μm section)</td>
<td>162 ± 26</td>
<td>134 ± 37 (4)</td>
<td>45 ± 34 (3)</td>
<td>41</td>
</tr>
</tbody>
</table>

*Memory and information test of Blessed et al, 1969.†Mean values ± standard deviation.

Table 2  Cholinergic activities‡ in human brain

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Choline Acetyltransferase (nmol/h/mg protein)</th>
<th>temporal</th>
<th>entorhinal</th>
<th>frontal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>occipital</td>
<td>parietal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3-50 ± 1-27</td>
<td>6-09 ± 1-37</td>
<td>4-64 ± 1-93</td>
<td>8-63 ± 3-61</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>4-44 ± 0-39</td>
<td>2-98 ± 0-30†</td>
<td>3-22 ± 1-52</td>
<td>7-67 ± 1-94</td>
</tr>
<tr>
<td>(a) mentally normal</td>
<td>0-91 ± 0-31†</td>
<td>1-31 ± 0-89†</td>
<td>1-21 ± 1-13†</td>
<td>2-94 ± 0-66†</td>
</tr>
<tr>
<td>(b) mentally impaired</td>
<td>0-97 ± 0-72</td>
<td>2-18 ± 1-78</td>
<td>0-56 ± 0-32</td>
<td></td>
</tr>
<tr>
<td>Combined Parkinson’s and Alzheimer’s disease**</td>
<td>1-42 ± 0-60†</td>
<td>1-08 ± 0-85†</td>
<td>1-10 ± 0-67†</td>
<td>1-91 ± 1-18§</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* †Significantly different (Student’s t-test) from the normal (p < 0.01 and <0.001).
‡Activities as mean ± standard deviation.
$Significant difference between the two Parkinsonian sub-groups (p < 0.05 in temporal cortex and p < 0.01 in the remaining areas), none of the differences between sub-group (b) and the group with Alzheimer’s disease reached significance.
**Statistics not performed on this group of 5 cases.
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remaining cases of Parkinson's disease, all of which were
cognitively impaired, the plaque count (23 to 41 per 1·3
mm²) and presence of neocortical neurofibrillary tangles
were diagnostic of co-existing Alzheimer's disease.
Amongst the seven cognitively impaired Parkinsonian
cases without co-existing Alzheimer's disease, the plaque
density was in the upper normal range (13 to 14 per 1·3
mm²) in three, including the two cases (see above) present-
ing primarily with a dementing disorder. In none of these
three cases with a relatively high plaque density were
neocortical tangles identified.

The neuron numbers in the nucleus of Meynert were
estimated in basal forebrain tissue (the substantia
innominata) dissected and paraffin embedded from the
formalin fixed left hemisphere as previously described.11
Serial sections 20 μm thick were cut through the entire
region and, at 500 μm intervals or less, the total number of
Meynert neurons (with a diameter greater than 25 μm and
containing a nuclear nucleolus) were counted (excluding
neurons adjacent to the diagonal band) between the levels of
the mid anterior commissure and the coronal level of the
mammillary body.17 From these counts the average
number of neurons per section was calculated. In selected
cases frozen tissue from the left temporal lobe was stained
histochemically for acetylcholinesterase (AChE) using
techniques described elsewhere.18

Biochemical analysis

At necropsy, samples of tissue were removed from the four
cortical lobes of the left hemisphere (Brodman areas: 10,
21, 28, 40 and 19) and stored in liquid nitrogen. For
biochemical analysis small portions of grey matter were
homogenized in 10 volumes of 0·32 M sucrose containing
0·5% Triton X-100 and assayed for CAT, AChE and pro-
tein as previously described.10 Analysis of the molecular
forms of the enzyme AChE was carried out on parietal
cortex, extracted and separated by sucrose density gradient
centrifugation, as previously described.16

Results

The different clinical categories (table 1) were
matched for age and post mortem delay. In all four
cortical lobes of the cognitively impaired Parkinsonian
cases there were reductions of CAT (table 2). In those Parkinsonian cases without clinically estab-
lished cognitive impairment, CAT activities were
less reduced and only significantly different from the
normal in occipital and parietal cortex. Comparing
the mentally normal and impaired Parkinsonian
subgroups, CAT activity in the latter was
significantly lower than the former in all areas
except occipital cortex. In the cases with combined
Parkinson's and Alzheimer's disease the enzyme
loss was generally similar to that in the separate
groups of demented Parkinson's and Alzheimer's
disease. In the latter group there were CAT reduc-
tions in all areas although interestingly these were,
with the possible exception of entorhinal cortex
(Brodman area 28), no greater than in the mentally
impaired Parkinsonian cases, despite the lesser
degree of dementia in the latter (table 1).

Similar although less marked changes were evi-
dent from the data on acetylcholinesterase activities
(table 2). Thus, there were in frontal, temporal and
parietal cortex losses of AChE in the Parkinsonian
group with dementia. This trend did not reach
significance in occipital cortex and in parietal cortex
there was no apparent distinction between this
group and the mentally normal Parkinsonian group.
The distinction between the mentally normal and
impaired Parkinsonian subgroups was generally less
marked for AChE, compared with CAT, and only
reached significance in entorhinal and frontal cortex.
As for CAT, AChE losses in the cases of combined
Parkinson's and Alzheimer's disease and in pure
Alzheimer disease cases were generally similar to
those in the demented Parkinsonian subgroup.
Furthermore, in the latter group there was an exten-
sive and selective loss of one molecular form of
AChE—the intermediate 10S form (fig 1). In the
deep three Parkinssianian cases analysed, this
form was reduced to 17% of the normal level whilst
the lower (3-7S) and higher (16S) molecular weight
forms were unaffected. Histochemically a loss of
cortical and white matter AChE positive cholinergic
fibres in a cognitively impaired Parkinsonian case is
illustrated in fig 2a and a lesser reduction in a case of
non-demented Parkinson's disease in fig 2b.

In view of the relationship known to exist in
Alzheimer's disease between the loss of cortical
CAT and extent of neuropathological abnormalities
such as plaques1 or tangles,4 the relation between
CAT loss and plaque density in the Parkinsonian

<table>
<thead>
<tr>
<th>Acetylcholinesterase (μmol/h/mg protein)</th>
<th>occipital</th>
<th>parietal</th>
<th>temporal</th>
<th>entorhinal</th>
<th>frontal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0·56 ± 0·20</td>
<td>0·95 ± 0·41</td>
<td>0·68 ± 0·15</td>
<td>1·18 ± 0·45</td>
<td>0·86 ± 0·17</td>
<td></td>
</tr>
<tr>
<td>0·38 ± 0·11</td>
<td>0·48 ± 0·14*</td>
<td>0·58 ± 0·13</td>
<td>1·23 ± 0·32</td>
<td>0·70 ± 0·08</td>
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<tr>
<td>0·39 ± 0·18</td>
<td>0·45 ± 0·09*</td>
<td>0·41 ± 0·17*</td>
<td>0·73 ± 0·21*§</td>
<td>0·44 ± 0·10§</td>
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<tr>
<td>0·43 ± 0·13</td>
<td>0·69 ± 0·28</td>
<td>0·31 ± 0·23</td>
<td>—</td>
<td>0·66 ± 0·75</td>
<td></td>
</tr>
<tr>
<td>0·46 ± 0·14</td>
<td>0·46 ± 0·15*</td>
<td>0·40 ± 0·12*</td>
<td>0·58 ± 0·32*</td>
<td>0·52 ± 0·18*</td>
<td></td>
</tr>
</tbody>
</table>
case was examined. There was, however, no correlation between the plaque numbers and activities of CAT or AChE in either the Parkinsonian cases or the normal and Parkinsonian groups together (r values were, respectively, -0.33, n = 14 and -0.31, n = 22 for temporal cortex CAT and 0.14 and -0.05 for temporal cortex AChE). In contrast, in the seven cognitively impaired Parkinsonian cases with available recent mental test scores, there was a tendency for CAT activities in the temporal cortex to be positively correlated with test scores (r = 0.84 p < 0.02). These data on the relation between CAT activities and mental test scores are illustrated in Fig 3 in which previous data, collected from cases with depression or Alzheimer-type dementia, are also incorporated. Figure 3 demonstrates that while there was a positive overall correlation between test scores and CAT, the relationship was nonlinear. Thus, a considerable loss (over 65% of the normal) of CAT was seen as the scores fall from normal (37) to around 20 but only a minor further reduction (under 20%) as test scores dropped further towards zero. Parkinsonian patients, therefore, with only slight or moderate cognitive impairment may have considerable loss of cortical CAT and Meynert neurons (see below).

Although cortical cholinergic activities in the Parkinsonian group were not apparently related to the presence of senile plaques in the cortex, they were clearly related to the numbers of neurons in the Meynert nucleus (Table 1). There was in the cognitively impaired Parkinsonian subgroup, where neuron numbers were available, an average 72% neuron loss—similar in extent to the cortical CAT loss, ranging from 66–78% in the different areas. In the cognitively unimpaired subgroup, neuron loss was less (average of 17%) in keeping with the less extensive cortical CAT reductions in this group, ranging from 11–60%. In the Parkinsonian group as a whole (including one case of combined Parkinson's and Alzheimer's disease) there were correlations between the number of neurons in the nucleus of Meynert and neocortical CAT activities in all areas except parietal cortex. This trend was most marked for temporal cortex (Fig 4) where the correlation was highly significant (p < 0.001) for the Parkinson cases (r = 0.93, n = 8). In the cases of Alzheimer's disease no such trend was apparent (Fig 4). There was in this moderately advanced series of Alzheimer cases only a slight loss of neurons from the Meynert nucleus compared with the control group, despite considerable reductions in cortical CAT, ranging from 59–82% in the different areas and in the four cases with available neuronal counts the correlation with temporal cortical CAT was near zero (r = 0.04). Although tissue atrophy no doubt occurs in areas affected by neuronal degeneration this was not (as judged by the length of the region containing identifiable Meynert neurons) in excess of 25% in the Alzheimer series and would not be expected to alter the non-significance of this correaltion. In future studies neuronal numbers in possible subgroups of the basal forebrain cholinergic cells and the extent of tissue shrinkage should be assessed together to obtain a more accurate index.
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Fig 2  Acetylcholinesterase (AChE) histochemically demonstrated in the superior temporal gyrus from a demented (a) and non-demented (b) case of Parkinson's disease. In (b) AChE-positive axonal cholinergic fibres are present in both white matter (W), the grey/white junction (arrow) and the deep cortical grey matter layers (G). In the grey matter of a typical demented Parkinsonian case (a) such fibre staining is absent (upper cortical layers not illustrated) although reactivity is still present in some pyramidal neurons and was observed in occasional white matter fibres. In both cases snap frozen tissue from the superior temporal gyrus was cryostat sectioned (20 μm), post-fixed in formal calcium and reacted histochemically for AChE using a silver intensification technique (see ref 17). Mag × 200 2a and 2b.
of Meynert neuronal degeneration.

Discussion

A loss of cortical CAT in Parkinsonian patients has previously been reported to correlate with the degree of dementia rated retrospectively. The present study reports a correlation between the enzyme loss, particularly in temporal cortex, and the severity of dementia rated shortly before death using a simple test of memory, learning, concentration and orientation. In occipital and parietal cortex, however, CAT activities in those patients without established cognitive impairment were also reduced compared with the normal, although not as greatly as in the assessed cognitively impaired group. With respect to the other cholinergic activity investigated, AChE, there was one of these areas (parietal cortex) no distinction between the impaired and unimpaired Parkinsonian group. Cholinergic abnormalities such as these in patients without gross mental abnormalities or obvious dementia raise the possibility that more subtle neocortical cognitive deficits may be a frequent feature of Parkinson's disease irrespective of more general cognitive function. Regarding deficits detected in the early stages of Parkinson's disease in shifting conceptual sets, will be of interest in future investigations to determine if these relate more specifically to frontal lobe deficits in dopamine as opposed to acetylcholine. Given the obvious limitations of the mental test employed in the present series there is clearly a need to conduct more comprehensive psychological assessment in combined clinical-pathological studies.

With respect to AChE reductions in dementia, the present investigation indicates that the loss of one particular molecular form of the enzyme is relatively more extensive than the loss of total activity. The data on parietal cortex suggest that, as in Alzheimer's disease, there is a selective loss of the intermediate (10S) form in demented cases of Parkinson's disease although it remains to be determined if this form is also substantially decreased in the non-demented cases. The extensive reduction in histochemical AChE fibre reactivity in the demented Parkinsonian cases is explicable in terms of loss of the predominantly membrane-bound 10S form which is probably present in cholinergic axonal processes. In general, there is no biochemical evidence to suggest that the cortical cholinergic abnormality differs functionally in the two dementing disorders and in both instances it probably reflects...
The extent of the cortical cholinergic abnormalities in cognitively impaired Parkinsonian patients, as judged by the reductions in CAT, is similar to that seen in Alzheimer’s disease. This is of considerable interest since dementia in the latter disorder is generally more severe than that seen in Parkinson’s disease. There are at least two possible explanations for this trend, which is illustrated (fig 3) by the much lower correlation between CAT activities and mental test performance below a score of approximately 20. In the first place, an abnormality of the cortical cholinergic system or loss of Meynert neurons may be associated with only a moderate deficit in cognitive function—as seen in some Parkinsonian cases and early Alzheimer-type dementia—but not with the severe mental deterioration and established dementia which eventually occurs in Alzheimer’s disease. Alternatively fluctuations in CAT enzymatic activity may not accurately reflect functional physiological changes in cholinergic neurotransmission. Reductions of up to 50% may occur, as in apparently mentally normal Parkinsonian cases, in the absence of alterations in synaptic transmission. Further analyses of the clinical deficits in Parkinson’s and Alzheimer’s disease in relation to not only cholinergic but also other transmitter activities may help to resolve this issue. In addition the influence of drug treatment and anticholinergic therapy which has not been considered in the present study, may need to be assessed in relation to the possible effects of levodopa on CAT and AChE.

From the therapeutic point of view patients with Parkinson’s disease showing cognitive impairment and cholinergic deficits may represent the optimum clinical group in which to assess the effects of cholinergic replacement or agonist therapy on countering cognitive deficits due to cortical cholinergic deficiency. In this group the relative absence of neocortical neuropathological abnormalities contrasts with the situation in Alzheimer’s disease, in which a cholinergic deficit is accompanied by extensive cortical neuropathological abnormalities (plaques and tangles) which may mask any potential improvement in cognitive function brought about by cholinomimetic therapy. Future electrophysiological studies should establish whether reported EEG abnormalities (random diffuse slow activity) in Alzheimer’s disease and presenile dementia and some cases of Parkinson’s disease, result from impaired cortical cholinergic function. Such a concept would find support in the reduced cortical electroencephalographic activity observed in rats with basal forebrain cholinergic lesions.

Although it is uncertain if the cholinergic deficit of Alzheimer-type dementia is causally or directly related to the presence of cortical plaques and tangles, it is clear from this series that the cortical cholinergic deficit in many cases of Parkinson’s disease is not explicable in terms of the development of cortical Alzheimer-type pathology. The most likely explanation for the extensive reductions in cortical CAT in Parkinson’s disease is degeneration of axonal processes associated with the extensive loss, reported here and elsewhere of neurons in the Meynert nucleus which supplies the neocortex with at least the majority of its cholinergic input. Whilst this nucleus is generally severely affected in presenile cases of Alzheimer’s disease, the cell loss in senile cases is only moderate and indeed was only slight in the four relatively less advanced senile cases of the present series. Despite this less extensive cholinergic cell body loss, cortical CAT activity in these Alzheimer cases was generally as extensively reduced as in the Parkinsonian group which showed a 70% neuron loss. It can therefore be suggested that cortical cholinergic abnormalities in Parkinson’s disease reflect the primary degeneration of neurons in the nucleus of Meynert. This may occur in an analogous, although unknown, fashion to the degeneration of pigmented nigral neurons. In Alzheimer’s disease the extensive cortical CAT reductions in conjunction with normal numbers of subcortical perikarya indicates, as argued previously, a “dying back” of cholinergic afferents—probably resulting from primary cortical pathology. In this context it is of interest to note that serotonergic-S2 receptor binding is reduced in Alzheimer-type but not Parkinsonian dementia, indicative, perhaps, of cortical abnormalities confined to the former disease.

The two cases of Parkinson’s disease who presented primarily with a dementing syndrome illustrate points of clinical and neuropathological interest. Psychiatrically, their presentation included neocortical cognitive deficits (the triad of aphasia, apraxia and agnosia) usually associated with Alzheimer’s disease and attributed to “parietal lobe” cortical pathology. This series demonstrates that in some patients aphasia, apraxia and agnosia may also be a feature of the cognitive impairment seen in Parkinson’s disease, and that in this respect the clinical presentation of these cases may mimic the dementia seen in Alzheimer’s disease. In such cases the diagnosis of Parkinson’s disease may not be obvious, especially if its usual presenting features of tremor, akinesia and rigidity are minimal. Such diagnostic difficulties have undoubtedly extended to combined clinical and neuropathological studies, in which neuropathological examination of patients
dying with suspected Alzheimer's disease has identified a small proportion lacking typical Alzheimer-type cortical changes. Examination of the substantia nigra in such cases is essential to identify, or exclude, Parkinson's disease. Establishing the neurochemical or neuropathological basis of the "parietal lobe" cognitive deficits seen in these cases of Parkinson's disease ideally requires investigation in a larger series. Neurochemically, however, it may be suggested that a neocortical cholinergic deficit is associated with parietal lobe symptomatology and that the deficit is reflected neuropathologically by loss of neurons in the nucleus of Meynert. A further interesting neuropathological feature in these cases was the presence of a neocortical senile plaque density in the upper normal range (14 plaques per 1-3 mm²) in the absence of neocortical tangles and of significant Alzheimer type pathology in the hippocampal formation. A similar subgroup of Parkinsonian patients with a moderate neocortical plaque density has been identified in a larger neuropathological series (Tomlinson and Perry, in preparation) and whilst the neuropathological criteria for diagnosing Alzheimer's disease, including the presence of neocortical tangles, were not present it remains possible that this density of senile plaque formation (either independently or in association with the cholinergic deficit; see above) contributes to the features of "parietal lobe" cognitive impairment. At a more basic pathogenetic level in this Parkinsonian subgroup, it remains to be determined if the aetiological factor(s) which cause or are associated with Parkinson's disease (including abnormalities in subcortical nuclei which project to the striatum and cortical regions) are responsible for inducing plaque but not tangle formation in the neocortex. The formulation of a hypothesis linking plaque formation with other pathological features of the disease however, such as Meynert neuron loss, does not readily account for the absence of a raised plaque density in the majority of Parkinsonian cases, with or without cognitive impairment.

In conclusion, the present investigation suggests a close correlation between mental impairment (or at least some aspects of the impairment) in Parkinson's disease and declining cholinergic activity, reflected by both cortical biochemical activities and subcortical neuronal population density. Other neuronal systems projecting to the cortex from various subcortical nuclei (such as the raphe and locus coeruleus) which also degenerate in Parkinson's disease should also be investigated in connection with the cognitive impairment of this disease.

The financial support of the Medical Research Council and excellent technical assistance of Dorothy Irving, Andrew Brown, Judith Thompson and Christine Lowthian are gratefully acknowledged.

References

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