A comparison of nerve cell loss in cortical and subcortical structures in Alzheimer's disease

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SUMMARY Loss of nerve cells from temporal cortex, hippocampus, nucleus basalis of Meynert and locus caeruleus was measured in 32 patients with Alzheimer's disease ranging from 48 to 92 years of age. Similar changes were present within the cerebral cortex and within the two subcortical structures.

Recent quantitative studies have shown that in Alzheimer's disease there is an atrophy and loss of large neurons from cerebral cortex and hippocampus and from subcortical areas such as nucleus basalis of Meynert (nBM) and locus caeruleus (LC). Because this conclusion is drawn from the findings of several independent research teams made on separate groups of patients usually of differing ages, and often using different counting techniques, it has not as yet been possible to assess how the extent of cell loss in any one of these affected regions compares with that in the other areas, within the same patients. In this study, we have addressed this question by comparing the extent of cell loss from cortical and subcortical regions of brain in 32 patients with Alzheimer's disease. These data bring together and correlate findings of ours on cell loss in Alzheimer's disease which have been published separately for each area of brain but have not previously been compared with each other.

Patients and methods

Brains were obtained at necropsy from 32 moderately to severely demented patients of age range 48–92 years (mean 73±6±3 years) dying with histologically verified Alzheimer's disease (see Mann et al for details of pathology). From the formalin fixed brains, tissue blocks were cut from topographically defined areas of temporal cortex (TCX), hippocampus, nBM and LC and from these paraffin sections were cut at 16 μm and 20 μm (LC) thickness and stained for RNA using Azure B. In these sections either the mean number of nucleated nerve cells per section was counted (nBM and LC) or the mean number of nucleated nerve cells per mm of tissue was estimated (TCX and hippocampus), as we have described elsewhere. The mean values of nerve cell number for these 32 patients together with age-matched control values taken from a series of 67 mentally able patients of age range 10–97 years are given for each area of brain in other reports and are, therefore, not reproduced here. For each patient percentage loss of nerve cells from each area was calculated by comparing actual patient values of cell counts with those expected for age alone (values derived from control data taken from 67 mentally able patients of age range 10–97 years published by us elsewhere). In this way the variable cell loss present in Alzheimer's disease due simply to growing old could be compensated for, and the extent of cell loss from each area of brain made more easily comparable.

Results

Although within each area of cortex and subcortex the extent of cell loss (for age) tended to decrease with increasing age (see also Mann et al), changes across both cortical and subcortical areas were broadly similar, either when taken overall for all 32 patients, or when considered at the different age categories (table). Overall, there was some tendency (p < 0.05) for cell loss in LC and TCX layer V to be greater than that in nBM and hippocampus, and this was largely a reflection of such a trend in the younger rather than the older patients (table). This broadly similar pattern of cell loss within cortex and subcortex was also seen in Spearman correlation statistics in which the extent of cell loss in one region was correlated with that in the others, for all 32 patients (LC with nBM, TCX III, TCX V and hippocampus; r =
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0.520 p < 0.001; r = 0.586 p < 0.001; r = 0.556 p < 0.001; r = 0.548 p < 0.001 respectively: nbM with TCX III, TCX V and hippocampus; r = 0.556 p < 0.001; r = 0.447 p < 0.01; r = 0.306 p < 0.05 respectively: TCX III with TCX V and hippocampus; r = 0.790 p < 0.001; r = 0.548 p < 0.001 respectively: TCX V with hippocampus r = 0.555 p < 0.001).

Discussion

The concept22 that a failure of subcortical systems using specific neurotransmitters underlies the cortical changes of Alzheimer’s disease is attractive because of its obvious therapeutic implications. However, the findings shown here that cortical nerve cells are damaged just as severely as those in the subcortex, together with other observations23 linking the degree of dementia with extent of degeneration in such large cortical cells, mean that equally important abnormalities are present in cortex as well as subcortex. The pathological relationship between the two regions may be primary, or secondary or may even co-exist in parallel. In this latter context it is possible that, because both cortical and subcortical neuron types show a similar neurofibrillary degeneration,4 5 13 15 19 21 a common and fundamental abnormality in all these four cell types may underlie the pathogenesis of Alzheimer’s disease. Evidence3 23–27 suggests that this abnormality may involve the ability of such cells to produce proteins appropriate to their correct physiological function.

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<table>
<thead>
<tr>
<th>Age class</th>
<th>n</th>
<th>Age (yrs)</th>
<th>Percentage loss of nerve cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Temporal cortex III</td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>6</td>
<td>58±3</td>
<td>74±6</td>
</tr>
<tr>
<td>65–74 years</td>
<td>7</td>
<td>69±6</td>
<td>±±3±3</td>
</tr>
<tr>
<td>75–84 years</td>
<td>12</td>
<td>80±0</td>
<td>±1±1</td>
</tr>
<tr>
<td>85+ years</td>
<td>7</td>
<td>88±0</td>
<td>37±2</td>
</tr>
<tr>
<td>All patients</td>
<td>32</td>
<td>73±6</td>
<td>57±1</td>
</tr>
</tbody>
</table>

Values are given as mean (±SEM) percentage nerve cell loss.
* * denotes significantly LESS than mean value in locus caeruleus p < 0.05, <0.01 respectively.
† denotes mean value significantly LESS than that in temporal cortex layer V p < 0.05.
‡ denotes mean for all 32 patients from refs 3 and 4.

References

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