Short report

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 studies¹⁻²¹ have shown that in Alzheimer's disease there is an atrophy and loss of large neurons from cerebral cortex¹⁻⁴ and hippocampus^{4,5} and from subcortical areas such as nucleus basalis of Meynert (nbM)⁶⁻¹⁵ and locus caeruleus (LC).¹⁵⁻²¹ 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^{3,4} 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 ± 3.0 years) dying with histologically verified Alzheimer's disease (see Mann *et al*⁴ for details of pathology). From the formalin fixed brains, tissue blocks were cut from topographically defined areas of temporal cortex⁴ (TCX), hippocampus,⁴ nbM¹⁵ and LC¹⁵ and from these paraffin sections were cut at $16 \mu\text{m}$ and $20 \mu\text{m}$ (LC) thickness and stained for RNA using Azure B. In these sections either

the mean number of nucleolated nerve cells per section was counted^{13,15,19,21} (nbM and LC) or the mean number of nucleolated nerve cells per mm^3 of tissue was estimated⁴ (TCX and hippocampus), as we have described elsewhere.^{4,13,15,19,21} 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 years⁴ are given for each area of brain in other reports^{3,4} 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 years⁴ and published by us elsewhere.^{4,15,19,21}) 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*^{4,15,21}), 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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Received 17 May 1985 and in revised form 24 August 1985.
Accepted 1 September 1985

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. Evidence^{3 23-27} suggests that this abnormality may involve the ability of such cells to produce proteins appropriate to their correct physiological function.

This work was supported in part by a grant to one of us (BM) from the North Western Regional Health Authority. We thank Mrs P Bellinger for the preparation of the manuscript.

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Table Comparison of nerve cell loss from five areas of brain in Alzheimer's disease

Age class	n	Age (yrs)	Percentage loss of nerve cells				
			Temporal cortex III	Temporal cortex V	Hippocampus	Locus caeruleus	Nucleus basalis
<65 years	6	58.3	74.6	70.4	69.1	86.2	61.7*
		±2.6	±3.3	±6.6	±8.4	±8.1	±5.9
65-74 years	7	69.6	65.0	65.5	39.5**†	79.7	59.0*
		±1.2	±3.7	±3.3	±10.2	±5.7	±4.6
75-84 years	12	80.0	55.4	57.2	49.7	53.8	41.9†
		±1.0	±2.6	±3.1	±6.7	±9.3	±5.8
85+ years	7	88.0	37.2	48.1	30.0	50.0	37.9
		±2.5	±6.5	±7.6	±7.5	±12.0	±8.3
All patients‡	32	73.6	57.1	59.5	46.8*†	64.2	48.5*†
		±3.0	±3.0	±2.7	±4.5	±5.4	±3.5

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.

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