

Short report

A comparison of changes in the nucleus basalis and locus caeruleus in Alzheimer's disease

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SUMMARY In 22 patients with Alzheimer's disease loss of neurons from the nucleus basalis of Meynert and locus caeruleus averaged 58% and 71% respectively with nucleolar volume being reduced by 30% in both. These changes were greater in those patients under 80 years of age and in such patients damage to the locus was more severe than that to the nucleus basalis. In older patients (over 80 years) changes were similar in extent in both regions

Reductions in activity of the enzyme markers choline acetyl transferase and dopamine β hydroxylase have been measured in the neocortex and hippocampus of patients with Alzheimer's disease.^{1–7} These changes probably result from a degeneration of the cholinergic nerve cells in the nucleus basalis of Meynert^{8–13} and in the septal nuclei¹⁴ and the noradrenergic neurons of the locus caeruleus.^{15–19} However, because this conclusion is drawn from several studies made by separate research teams on different groups of patients it has not been possible to evaluate the relative extent to which these two transmitter systems are damaged in the same patients with Alzheimer's disease. We have assessed this by counting the number of nerve cells in nucleus basalis and locus caeruleus and by measuring the volume of their nucleolus (an index of ribosomal-RNA synthesis which relates²⁰ to the level of nerve cell activity).

Patients and methods

Brains were obtained at necropsy from 22 moderate to severely demented patients of age range 48–92 years (mean 74.9 ± 2.5 years) dying with histologically verified Alzheimer's disease. Care was taken to exclude from the study any patient in whom vascular disease might have led to significant brain damage. From the formalin fixed brains tissue blocks were cut to include the most extensive part of nucleus basalis (that is that between optic tract and anterior commissure) and the central part of locus caeruleus. From these two blocks five paraffin sections

were cut at 16 and 20 μm thickness respectively and stained for RNA using Azure B. In these the total number of nucleolated nerve cells were counted^{8,16,19} in nucleus basalis and locus caeruleus and the average number per section per patient calculated. Nucleolar volume was measured¹⁵ in 60 nerve cells of each type. For each patient percentage loss of nerve cells from nucleus basalis and locus caeruleus and the percentage reduction in nucleolar volume in those remaining were calculated by comparing actual patient values of cell number and nucleolar volume with those expected for age alone (derived from control data published elsewhere^{11,19}).

Results

In the 22 patients with Alzheimer's disease loss of nerve cells from nucleus basalis ranged from 31.4%–76.4% (mean $57.7 \pm 2.7\%$) (table). Cell loss from locus caeruleus was more variable ranging from 6.8% to 98.3% with the average loss of 71.2% ($\pm 5.4\%$) being significantly greater ($p < 0.05$) than that in nucleus basalis. Reduction in nucleolar volume in remaining nerve cells of each type ranged from 10 to 60% with the mean reduction being about 30% in both (table). Overall, regression analysis showed only weak relationships between cell loss in locus caeruleus and nucleus basalis ($r = 0.329$; $0.1 > p > 0.05$) and reductions in nucleolar volume in both cell types ($r = 0.485$; $p < 0.05$).

Patients were subgrouped into a younger group aged under 80 years (group 1) and an older group over 80 years (group 2); mean values for each feature in both groups were calculated and compared by the *t* test (table). In group 1 patients the loss of nerve cells and the reduction in nucleolar volume were both greater in locus caeruleus and nucleus basalis than was measured in group 2 patients

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Table Mean percentage loss of cells from and reduction in nucleolar volume in remaining cells of locus caeruleus and nucleus basalis in 22 patients with Alzheimer's disease for whom age and duration of illness is also shown. Overall mean values and mean values for group 1 and group 2 patients are also given

Patient	Age (yr)	Duration (yr)	Locus caeruleus		Nucleus basalis	
			% loss of cells	% reduction in nucleolar volume	% loss of cells	% reduction in nucleolar volume
1	48	5	91.7	48.2	73.7	53.1
2	53	7	93.8	52.5	59.6	53.1
3	55	3	96.5	49.9	76.9	25.3
4	63	4	97.6	47.9	70.2	48.9
5	66	1	71.2	34.8	68.6	16.4
6	68	3	98.3	66.5	76.4	53.2
7	71	7	56.8	30.5	64.2	57.7
8	72	2	92.6	22.2	61.0	18.6
9	73	4	80.4	31.6	68.6	44.2
10	75	4	78.2	19.9	49.1	33.2
11	75	5	93.0	30.3	56.3	24.4
12	78	11	94.9	42.1	40.2	14.9
13	80	4	41.1	16.0	70.0	47.7
14	82	7	84.7	34.2	48.4	9.6
15	83	3	60.8	17.9	44.3	10.5
16	84	9	58.8	21.9	59.8	20.9
17	84	6	6.8	12.7	48.2	18.7
18	85	5	33.2	19.3	53.4	20.7
19	86	5	38.5	31.3	59.1	25.8
20	88	3	64.1	27.9	44.3	10.5
21	89	2	83.0	28.6	59.4	19.2
22	92	4	48.5	19.2	31.4	13.0
Overall Mean	74.9 ±2.5	5.2 ±0.5	71.2±5.4§	32.1±3.0	57.7±2.7	29.4±3.5
Group 1 Mean Patients	66.4† ±2.5 1-12	5.6 ±0.6	87.1†¶ ±3.7	39.7† ±4.0	63.7* ±3.2	36.9† ±4.7
Group 2 Mean Patients	85.3 ±1.1 13-22	4.8 ±0.6	52.0±7.5	22.9±2.3	51.8±3.4	19.7±3.6

* † ‡ denotes group 1 value significantly greater than corresponding group 2 value, $p < 0.05$, < 0.01 , < 0.001 respectively.

§ ¶ denotes mean value in locus caeruleus significantly greater than corresponding value in nucleus basalis, $p < 0.05$, < 0.001 respectively.

(table). Moreover, in group 1 patients cell loss from locus caeruleus was significantly greater than that from nucleus basalis, whereas in group 2 patients the loss was the same in both cell types. Reductions in nucleolar volume were the same in each cell type in either group (table).

Discussion

From this study two main points emerge. Firstly, damage to subcortical structures in Alzheimer's disease is usually greater in younger persons. This is in keeping with other studies^{8,9,12,18} in which a more extensive cell loss was reported in nucleus basalis^{8,9,12} and locus caeruleus¹⁸ in younger patients and also explains why decreases in choline acetyl transferase activity in the cerebral cortex in Alzheimer's disease are age dependant.³⁻⁵ This same inverse relationship with age is seen with other pathological changes such as frequency of plaques and tangles in neocortex (Mann-unpublished obser-

vations) and also at the level of the whole brain where ventricular enlargement becomes less frequent²¹ and cortical atrophy becomes less severe and usually confined to temporal lobes,²² in old people with Alzheimer's disease. Whether this greater damage in younger patients reflects a more severe disease process is not clear. Bowen²³ speculated that the older patients may die at an earlier stage of the illness, though the failure to demonstrate any significant difference in duration between our group 1 (young) and group 2 (old) patients implies that this is not so and that the pathological differences represent a more severe expression in the younger patients. Secondly, the extent of damage to locus caeruleus is greater in younger patients than that to nucleus basalis whereas in older patients the damage is similar in both regions. Certain clinical features such as aphasia, apraxia and agnosia, extrapyramidal signs, seizures and personality and behavioural changes have been said²⁴ to distinguish the younger patient with Alzheimer's disease though other

studies²⁵ have not corroborated this. A more recent report²⁶ indicates a greater prevalence of language disturbance and a disproportionate degree of left-handedness among younger patients which may be related to a heightened vulnerability of the left hemisphere. Therefore, while disturbances in the cholinergic system are thought to relate specifically to the impairment of cognitive functioning of Alzheimer's disease,²⁷ it is possible that an especially severe degeneration of the noradrenergic system in younger patients is associated with the presence of certain of these other neurological changes.

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