CLINICAL RESEARCH

Neurochemical characteristics of early and late onset types of Alzheimer's disease

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Abstract

Brains of 49 patients who had died with Alzheimer's disease and 54 controls were examined. The Alzheimer group exhibited noticeably reduced activity of the cholinergic marker enzyme choline acetyltransferase in the cerebral cortex, but cortical concentrations of noradrenaline, γ-aminobutyric acid, and somatostatin were also significantly reduced. Analysis of the results according to age at death showed that the older patients, dying in their 9th and 10th decades, had a relatively pure cholinergic deficit confined to temporal lobe and hippocampus, together with a reduced concentration of somatostatin confined to temporal cortex. By contrast, the younger patients, dying in their 7th and 8th decades, had a widespread and severe cholinergic deficit together with the abnormalities of noradrenaline, γ-aminobutyric acid, and somatostatin, and the younger patients accounted for most of the abnormalities in these systems observed in the overall group. Comparison of the young subjects with Alzheimer's disease with the older controls did not support the concept of Alzheimer's disease representing an acceleration of the aging process.

These results suggest that Alzheimer's disease in people aged under 80 may represent a distinct form of presenile dementia which differs in important respects from the dementia of old age.

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Introduction

Alzheimer's disease is the commonest cause of dementia and is rarely seen below the age of 50. The distinctive histopathological features of abundant neocortical senile plaques and neurofibrillary tangles are found both in young and in old patients, and hence it is no longer usual to make a distinction between presenile dementia in patients below 65 and senile dementia of Alzheimer type in the older patient. Nevertheless, although the histopathological features are qualitatively similar, the younger patient exhibits more severe and widespread histological abnormalities[1-4] and clinically a more rapid course with a prominence of dysphasias, apraxias, and agnosias.[5,6]

Neurochemical analysis of postmortem brain and cortical biopsy tissue samples has contributed to an improved understanding of the selectivity of neuronal degeneration. Several studies have confirmed that reduced activity of the cholinergic marker enzyme choline acetyltransferase in the cerebral cortex is a consistent feature of Alzheimer's disease.[7,8] The reduced activity of the enzyme is believed to reflect damage to the ascending cholinergic projection from nucleus basalis to the cortex,[8-10] and the extent of loss of activity correlates both with the severity of dementia and with the density of cortical senile plaques.[11] In common with the histopathological changes, the cholinergic abnormality is most severe in the youngest patients[12-14] and in the older patient spares the frontal cortex.[15]

In addition to the cholinergic deficit there is also evidence for damage to the ascending noradrenergic system in Alzheimer's disease.[16,17] Bondareff *et al* reported a dramatic loss of cells from the nucleus of origin of the cortical noradrenergic projection (locus coeruleus) in a group of young patients with severe dementia of Alzheimer type,[18] suggesting that, as with the cholinergic damage, the changes may be most pronounced in the younger patients. In other studies markers of intrinsic cortical neurones have been examined. Normal concentrations of cholecystokinin and vasoactive intestinal polypeptide have been reported, but reduced concentrations of γ-aminobutyric acid and somatostatin are observed, particularly in the temporal lobe.[8] These changes may reflect the reduced numbers of cortical neurones in Alzheimer's disease[4,19]; again the cell loss is most severe in the younger patients.[4]

To study further the differences in the patterns of neuro-

chemical abnormalities in young versus old patients with Alzheimer's disease we have analysed choline acetyltransferase, noradrenaline, γ-aminobutyric acid, and somatostatin values in a large necropsy series of young (aged <79) and old (aged >79) patients with Alzheimer's disease and a group of controls.

Methods

We examined 49 brains from patients dying with Alzheimer's disease (mean age 78·2 (SD 9·4) years; mean delay before necropsy 39·8 (SD 23·9) hours) and 54 brains from controls (mean age 81·1 (SD 7·8) years; mean delay before necropsy 54·8 (SD 23·7) hours). Brains were divided midsagittally for subsequent biochemical and histological analyses.[14] All of the subjects with Alzheimer's disease had been rated clinically during life,[20] and histological examination of necropsy tissue confirmed the presence of widespread neocortical senile plaques and neurofibrillary tangles. Necropsy tissue from the controls was also examined histologically and was normal.

The following areas were dissected for analysis: amygdala, posterior hippocampus, frontal cortex (Brodmann area 10), temporal cortex (Brodmann area 21), parietal cortex (Brodmann area 7), and occipital cortex (Brodmann area 17). Tissue samples were homogenised in water for determination of choline acetyltransferase activity[21] and γ-aminobutyric acid concentration.[22] Tissue from the same brains was also extracted in perchloric acid for subsequent separation of dopamine and noradrenaline using an HPLC system and measurement with electrochemical detection.[23] Samples for somatostatin radioimmunoassay were extracted in boiling 0·5M acetic acid before determination of immunoreactivity.[24]

In order to stabilise the variance within groups and normalise distributions the biochemical data were transformed logarithmically and comparison between groups made using a two tailed *t* test with either pooled or separate variance estimates, as appropriate. In view of the large number of comparisons made a probability value of <0·02 was taken as significant.

Results

There was a highly significant ($p<0·001$) reduction in choline acetyltransferase activity in all areas of the brains examined in the subjects with Alzheimer's disease (table I). This was most pronounced in the temporal cortex, where enzyme activity was reduced to 38% of the control value. The concentration of γ-aminobutyric acid was also reduced ($p<0·01$) in the temporal lobe but not in other cortical areas. Somatostatin concentration was reduced in both the frontal cortex (71% of control value; $p<0·01$) and in the temporal cortex (43% of control value; $p<0·001$). Noradrenaline and dopamine values were determined in the same group and will be reported separately.

In an earlier report of choline acetyltransferase and γ-aminobutyric acid measurements from the first 25 cases of Alzheimer's disease and 26 controls in this series we analysed the effect of age at death by dividing the group on the basis of the median age of 79 years.[14] This served to distinguish the different patterns of change in choline acetyltransferase activity in young and old patients with Alzheimer's disease, and we therefore used this age to separate our subjects into young (<79 years at death) and old (>79 at death) in the present study. The mean dementia scores did not differ significantly between the two age groups (14·0 (SD 3·0) in the young; 12·3 (SD 4·7) in the old). All were disorientated in time and place, and most were unable to feed themselves or were incontinent, or both, owing to their dementia. Most of the patients with dementia had suffered a prolonged terminal illness with bronchopneumonia. There was no difference between young and old when the mode of death was classified as a prolonged terminal illness or sudden death.[14] Similarly,

TABLE I—*Neurochemical changes in brains of patients with Alzheimer's disease and matched controls. Figures are means (SEM) of logarithmically transformed data [medians of untransformed data in square brackets]*

		Choline acetyltransferase (pmol/h/g protein)	% of control value	γ-Aminobutyric acid (pmol/h/g protein)	% of control value	Somatostatin (pmol/h/g protein)	% of control value
Amygdala	Controls (n = 48)	1·52 (0·04) [31·2]	43	1·30 (0·02) [20·1]	83		
	Patients (n = 46)	1·15 (0·05) [11·5]***		1·22 (0·03) [16·1]*			
Hippocampus	Controls (n = 44-50)	1·15 (0·03) [14·2]	47	1·33 (0·03) [19·0]	76		
	Patients (n = 31-44)	0·82 (0·05) [6·7]***		1·21 (0·03) [15·2]**			
Frontal cortex	Controls (n = 26-53)	0·78 (0·02) [6·2]	59	1·13 (0·03) [11·5]		1·92 (0·03) [79·6]	71
	Patients (n = 29-49)	0·55 (0·03) [3·7]***		1·07 (0·02) [11·0]		1·77 (0·04) [61·2]**	
Temporal cortex	Controls (n = 25-53)	0·79 (0·02) [6·0]	38	1·24 (0·03) [16·6]	81	2·18 (0·03) [157·8]	43
	Patients (n = 31-47)	0·37 (0·04) [2·1]***		1·15 (0·02) [13·7]**		1·81 (0·04) [62·8]***	
Parietal cortex	Controls (n = 52)	0·71 (0·02) [5·3]	59	1·21 (0·02) [15·8]			
	Patients (n = 48)	0·48 (0·04) [2·9]***		1·22 (0·02) [16·7]			
Occipital cortex	Controls (n = 53)	0·53 (0·19) [3·6]	56	1·34 (0·02) [20·2]			
	Patients (n = 48)	0·28 (0·04) [1·9]***		1·33 (0·02) [20·5]			

*p<0·02, **p<0·01, ***p<0·001.
Noradrenaline determined in same series (Rossor *et al*, unpublished) was found to be significantly (p<0·02) reduced in Alzheimer group in hippocampus, frontal cortex, and cingulate cortex.

TABLE II—*Neurochemical changes in brains of young and old patients with Alzheimer's disease expressed as percentage of age matched control value. (Controls comprised 35 young and 19 old subjects: Alzheimer group comprised 23 old and 26 young subjects)*

	Choline acetyltransferase	Noradrenaline	γ-Aminobutyric acid	Somatostatin
		Young patients (age <79)		
Amygdala	35***		72*	
Hippocampus	42***	50***	59***	
Frontal cortex	42***	59	65**	59**
Temporal cortex	30***	50*	62***	35***
Parietal cortex	50***		89	
Occipital cortex	51***		81	
Cingulate cortex		39***		
		Old patients (age >79)		
Amygdala	51***		93	
Hippocampus	51***	87	91	
Frontal cortex	78	65	107	83
Temporal cortex	47***	95	98	51***
Parietal cortex	69**		112	
Occipital cortex	65**		112	
Cingulate cortex		92		

*p<0·02. **p<0·01. ***p<0·001.

although many patients had received benzodiazepines, antibiotics, and neuroleptics, the drug histories did not differ between the two groups.

In those patients dying above the age of 79 the neurochemical abnormality was confined to changes in the cholinergic system and a reduced concentration of somatostatin in the temporal cortex (table II). Moreover, the cholinergic damage was not uniformly distributed—that is, there was a relative sparing of the frontal cortex. No differences were discernible in the γ-aminobutyric acid, somatostatin, or noradrenaline systems.

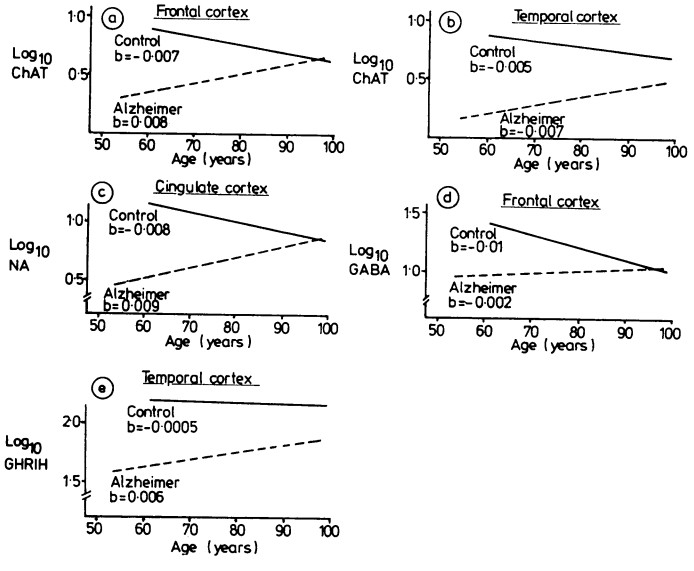
Analysis of brains of the younger (aged <79 at death) subjects with Alzheimer's disease showed more profound and widespread neurochemical changes, with losses of choline acetyltransferase and somatostatin from all cortical areas examined compared with age matched controls. Both the cholinergic and somatostatin abnormalities affected the frontal cortex in this younger group. In addition, the γ-aminobutyric acid concentration was reduced in amygdala, hippocampus, temporal cortex, and frontal cortex, and noradrenaline was significantly reduced in the hippocampus ($p<0.001$), temporal cortex ($p<0.02$), and cingulate cortex ($p<0.001$).

Changes of neurotransmitter markers with age in the control group were confined to reductions in the cholinergic and γ-aminobutyric acid systems in some areas with advancing age. Table III summarises the significant differences between young and old controls and young and old subjects with Alzheimer's disease. All values in the older Alzheimer group tended paradoxically to be higher than in the younger subjects with the disease, and the difference in choline acetyltransferase activity was significant ($p<0.02$) in the frontal cortex, where there was a reversal of the decline in activity seen with age in the control group. Regression analyses of biochemical data on age confirmed a significant decline of choline acetyltransferase activity with age in the controls in the frontal cortex (regression coefficient $b=-0.0067\pm0.0019$; $p<0.01$) and of γ-aminobutyric acid concentration with age in the frontal cortex ($b=-0.011\pm0.0034$; $p<0.01$) and temporal cortex ($b=-0.0088\pm0.0031$; $p<0.01$). By contrast, in the Alzheimer group regression analysis confirmed an increase of choline acetyltransferase activity with age in the frontal cortex ($b=+0.0086\pm0.0034$; $p<0.02$). Comparison of slopes of regression lines between control and Alzheimer groups[25] showed the following to be significantly different: choline acetyltransferase activity in frontal cortex ($p<0.01$), γ-aminobutyric acid concentration in frontal cortex ($p<0.01$) and temporal cortex ($p<0.01$), and noradrenaline concentration in cingulate cortex ($p<0.01$). The figure gives representative examples of regression lines.

TABLE III—*Significant differences ($p<0.02$) between young and old controls and young and old patients with Alzheimer's disease. Figures are means (SEM) of logarithmically transformed data [medians of untransformed data in square brackets]*

	Young (age <79)		Old (age >79)		% of young values
Controls					
Choline acetyltransferase, frontal cortex	0·85 (0·02) [7·0]	(n = 19)	0·75 (0·02) [5·6]	(n = 35)	79***
γ-Aminobutyric acid: Hippocampus	1·42 (0·05) [24·6]		1·27 (0·03) [17·2]		71**
γ-Aminobutyric acid: Frontal cortex	1·23 (0·05) [17·0]		1·07 (0·03) [10·7]		69**
γ-Aminobutyric acid: Temporal cortex	1·33 (0·05) [20·1]		1·19 (0·03) [15·2]		72**
Patients with Alzheimer's disease					
Choline acetyltransferase, frontal cortex	0·47 (0·05) [2·8]	(n = 22-26)	0·64 (0·04) [4·6]	(n = 17-23)	148**
Noradrenaline, cingulate cortex	0·65 (0·05) [3·8]		0·87 (0·07) [6·6]		166*

*p < 0·02. **p < 0·01. ***p < 0·001.



Regression analyses of logarithmically transformed biochemical data with age for controls and patients with Alzheimer's disease. (a) Choline acetyltransferase (ChAT) activity in frontal cortex. (b) Choline acetyltransferase activity in temporal cortex. (c) Noradrenaline (NA) concentration in cingulate cortex. (d) γ-Aminobutyric acid (GABA) concentration in frontal cortex. (e) Somatostatin (GHRIH) immunoreactivity in temporal cortex.

To address the question whether the changes in Alzheimer's disease represent an acceleration of a series of declines in neurotransmitter values with age, we compared subjects in the young Alzheimer group with old controls. In each instance where a significant reduction in choline acetyltransferase activity or somatostatin concentration had been observed compared with age matched young controls a significant ($p<0.01$) reduction was also observed when the comparison was made with the older control group. Noradrenaline concentration in the cingulate cortex was also lower in the young Alzheimer group when compared with old controls but none of the γ-aminobutyric acid concentrations was significantly different.

Discussion

Necropsy and biopsy studies have shown that the severity of the cholinergic deficit in Alzheimer's disease is age related. Bowen *et al* reported a greater reduction in choline acetyltransferase activity of the whole temporal lobe in patients aged 70-80 than in those dying at a later age,[12] and Davies reported a similar observation in the frontal, parietal, and temporal cortex.[13] Our data confirm these and our earlier observations[14] of a more profound cholinergic deficit in younger patients. Moreover, the sparing of the frontal cortex in older patients[15] remains a consistent pattern in the larger series.

The noradrenergic system, another ascending projection to the cortex, has also been implicated in the pathophysiology of Alzheimer's disease. Both noradrenaline[16] and the biosynthetic marker enzyme dopamine-β-hydroxylase[17] are reduced in necropsy samples of cerebral cortex. We have confirmed a noradrenergic deficit, most readily detectable in the noradrenaline rich cingulate cortex. The noradrenergic abnormality, however, was significant only in the younger age group, which accords with the description of Bondareff *et al* of a pronounced loss of presumed noradrenergic cells from the locus coeruleus in a group of patients who died at an early age[18]—although more recently we also observed a loss of noradrenergic cells from this nucleus in a small group of elderly patients with Alzheimer's disease.[26]

Histological studies have shown a loss of cortical neurones in Alzheimer's disease when compared with age matched controls.[4 19 27] Several earlier studies, however, failed to detect a significant neuronal loss; this may have related to the age

distribution of the patients studied, since Mountjoy *et al* did not observe any significant differences in cortical neuronal counts among patients with Alzheimer's disease aged over 80 but confirmed that neurones were lost in younger patients.[4] This agrees with earlier studies in which the histopathological changes in presenile Alzheimer's disease were more severe than in senile dementia.[1 2] With the exception of somatostatin,[28 29] changes in intrinsic biochemical cortical markers are not prominent.[8] Other studies have reported small changes in the concentration of γ-aminobutyric acid but unaltered concentrations of vasoactive intestinal polypeptide and cholecystokinin immunoreactivities.[8] In our study there were significant reductions of γ-aminobutyric acid in both frontal cortex and temporal lobe structures, but these were confined to the younger subjects dying with Alzheimer's disease. The somatostatin deficit was also found in both the frontal cortex and temporal cortex in the younger group, whereas it was confined to the temporal cortex in the older group. This accords with the observation of Hubbard and Anderson that atrophy in patients with Alzheimer's disease dying over the age of 80 is confined to the temporal lobe.[3] We have previously reported a reduction in somatostatin concentration in the temporal cortex in Alzheimer's disease,[29] in contrast to the more widespread abnormality reported by Davies *et al*.[28] Probably this reflects the different age distribution of the patients in the two studies.

The age range of the control group (61-97) was relatively narrow but did permit a limited analysis of changes in neurotransmitters and neuropeptides in normal aging. As in other studies[14 30] we found these to be modest. The only area to show a significant decline in choline acetyltransferase activity with age was the frontal cortex; this agrees with some previous studies,[12 14] but we could not confirm the dramatic reductions in cortical choline acetyltransferase activity with age reported by Davies.[13] γ-Aminobutyric acid concentrations declined significantly with age in the frontal and temporal cortex, as reported in earlier studies.[15 30] It has been suggested that Alzheimer's disease may reflect an acceleration of the normal aging process, but these results provide little support for this view. The losses of noradrenaline and somatostatin seen in Alzheimer's disease are not features of normal aging, and there are relatively few changes in cholinergic systems with age. Moreover, choline acetyltransferase activity in the young subjects dying with Alzheimer's disease was significantly different from that in the old control group. Thus the neurochemical profile in Alzheimer's disease cannot be said to resemble that of the aged brain as a result of premature aging.

The explanation for the differences in the patterns of neurochemical abnormality between the young and old cases of Alzheimer's disease is not readily apparent. Possibly the older patients succumbed to intercurrent illness earlier in the disease, although the severity of dementia was similar in the two groups. Alternatively, the neurotransmitter abnormalities may reflect a nosological distinction between early and late onset Alzheimer's disease.[31] The older patient exhibits a relatively pure abnormality of the ascending cholinergic projection, most severe in temporal lobe, with an additional loss of somatostatin from temporal cortex. The complex pattern of neurotransmitter and neuropeptide abnormalities in younger patients with the disease might be expected to militate against the possible success of simple cholinergic replacement as treatment, although this might be predicted to be more likely to succeed in elderly patients.

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