Letters


Plaques and tangles and transmitter deficiencies in dementia

Sir: In Alzheimer type dementia there is a degeneration and loss of the central noradrenergic neurons of the locus caeruleus1 associated with which are reductions in brain norepinephrine concentration1,4 and dopamine β hydroxylase activity,6 together with decreased 3-methoxy-4-hydroxyphenyl levels in both brain and urine.8 Recent reports9 suggest that within the broad spectrum of patients with Alzheimer type dementia, there exist subgroups, characterised by either a severe, or a milder loss, of neurons from the locus caeruleus. Furthermore, a more severe dementia and an earlier death have both been noted in those cases where cell loss is extreme,3 though these differences are not seemingly associated with extra reduction in dopamine-β-hydroxylase activity or 3-methoxy-4-hydroxyphenyl glycol levels.7 This apparent anomaly is explained by the occurrence, in these more severely affected cases, of a possible compensatory ingrowth of noradrenergic fibres from areas other than the locus caeruleus, in response to the more extensive loss of these latter cells. Other studies,3 report that norepinephrine concentration is also reduced in patients with Down's syndrome, when the Alzheimer type of pathology is present, and suggest that loss of noradrenergic activity is a feature specific to Alzheimer type dementia.

We have investigated the brains of patients with Alzheimer type dementia, in whom there were variable losses of locus caeruleus neurons, for evidence that extra impairment of function may occur in those cases where cell loss was more severe. We have also examined for changes in locus caeruleus neurons the brain of a patient with Down's syndrome, and the brains of retired professional boxers with dementia pugilistica, in which the extensive neurofibrillary degeneration of nerve cells, in contrast to Alzheimer type dementia is not accompanied by significant senile plaque formation.

Brains were obtained from 19 cases of Alzheimer type dementia (mean age 84.7 ± 1.1 years) one case of Down's syndrome (age 59 years) and from four retired boxers (mean age 56.5 ± 1.3 years). Two separate groups of patients, matched for age and sex, and dying free of neurological or psychiatric disease, were controls and these totalled 21 patients (mean age 85.1 ± 1.1 years) and 16 patients (mean age 55.9 ± 1.3 years) respectively. The number of nucleolated nerve cells per 20 μm section was counted5 and the volume of the nucleus in remaining nerve cells was measured,1 in the locus caeruleus, on both sides, in all 60 cases. Statistical comparisons were made using Student t test.

Overall, the mean number of nucleolated nerve cells in the 19 cases of Alzheimer type dementia (Group 3) was reduced by 55%, and the nucleolar volume of residual cells was also significantly reduced by 20%, when compared with values from the control group (table). Values of cell number and nucleolar volume in those cases of Alzheimer type dementia where counts of locus caeruleus nerve cells fell below 30 per section (Group 1) were analysed separately from the remaining cases (Group 2), where such counts exceeded this figure (table). The only significant difference found between the two groups was in cell counts. Therefore, it seems that, in Alzheimer type dementia groups, the capacity of remaining cells to form proteins is equally reduced, irrespective of the actual number of cells that are still present. Categorisation of Alzheimer type dementia cases into subgroups, based on changes in cell number in locus caeruleus alone is arbitrary since reductions in functional integrity of the locus caeruleus cell group are probably, therefore, more closely related to changes in function within individual cells rather than decreases per se in overall cell number. It is probably for this reason, rather than compensatory ingrowth, that similar dopamine-β-hydroxylase and 3-methoxy-4-hydroxyphenyl glycol values were recorded by Perry and colleagues,7 in both their subgroups.

In the Down's syndrome case there was a virtually complete loss of nerve cells from the locus caeruleus and the few that remained (numbering 4-6 per 20 μm section; about 5% of control number of 90-8) contained large globose neurofibrillary tangles. Nucleolar volume, in these residual cells, was reduced by 28%, from a control value of 69-1 μm3 to one of 49-9 μm3. Decreases in brain concentration of norepinephrine in Down's syndrome6 would seem, therefore, to be due to loss and atrophy of cells in the locus caeruleus, as is the case in Alzheimer type dementia.

In the four cases of dementia pugilistica the mean number of nerve cells in the locus caeruleus was 29-8 ± 1-7, which was significantly less (p < 0.001) than the 90-8 ± 1-4 counted in the control group. Nucleolar volume in the remaining cells was

| Table Changes in locus caeruleus nerve cells in Alzheimer type dementia: mean ± sem |
|---------------------------------|-----------------|------------------|------------------|------------------|
|                                | Normal (n = 21) | Group 1 (n = 9) | Group 2 (n = 10) | Group 3 (n = 19) |
| Locus caeruleus neuron numbers | 75.8 ± 3.2      | 21.9 ± 1.9*     | 45.4 ± 4.7*     | 34.3 ± 3.8*     |
| (Mean/20 μm section) Nucleolar volume (μm³) | 69.9 ± 1.0      | 55.3 ± 2.6*     | 57.8 ± 2.5*     | 56.6 ± 1.8*     |
| Brain weight (g)              | 1205.2 ± 25.2   | 1137.2 ± 38.7   | 1160.8 ± 1.2    | 1149.6 ± 24.7   |
| Sexes                         | M               | F               | 5                | 7                |
| Age at death (yr)             | 85.1 ± 1.1      | 83.9 ± 1.8      | 85.8 ± 1.2      | 84.7 ± 1.1      |

*Significantly (Student t test) different from normal at p < 0.001. The only significant difference between group 1 and group 2 cases of Alzheimer type dementia was between locus caeruleus counts (p < 0.001).
51·2 ± 1·4 μm³, which was also significantly less (p < 0·001) than that of 69·1 ± 1·3 μm³ measured in the controls. Reductions in nerve cell number and nucleolar volume of 67% and 26% respectively, are similar to these decreases in Alzheimer type dementia and Down’s syndrome and may be presumed, therefore, to lead to substantial depletion of brain noradrenaline in this condition also.

It therefore seems that loss of noradrenergic activity is found in all those dementia characteristics by a neurofibrolular degeneration of nerve cells even though senile plaques may not always be present. The alterations in protein synthesis that lead to formation of paired helical filaments have been related to the presence of toxic substances, particularly aluminium, within the brain, which may accumulate from an altered permeability of the microvasculature, stemming from loss of modulation by noradrenergic fibres. Changes in cholinergic activity, similar to those in Alzheimer type dementia, and Down’s syndrome, occur in scrapie, a slow virus disease affecting sheep and goats, in which amyloid plaques, similar to senile plaques, but not neurofibrolular changes, are present in the brain. This suggests that alterations in the cholinergic rather than noradrenergic neurotransmitter system may be fundamental to plaque formation in ATD and Down’s syndrome, a conclusion strengthened by the close quantitative relationship that occurs between reductions in choline acetyltransferase activity and frequency of senile plaques in cases of Alzheimer type dementia.

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References

Progressive spastic paraplegia due to persistent echo virus encephalomyelitis in a child with X-linked hypogammaglobulinaemia

Sir: We wish to describe a boy who presented with signs of a progressive spastic paraplegia and was found to suffer from hypogammaglobulinaemia and chronic encephalitis due to Echo virus type 29. Intact T cell function was indicated by the lymphocytic infiltrates in the CNS and by lymph nodes depleted of lymphocytes and with absent reactive follicles in the vestibial germinat centres. Although there was no family history in our patient, his age, sex and persistent encephalitis suggest the X-linked form of hypogammaglobulinaemia. The particular points of interest in this case are absence of frequent infections and preservation of normal intelligence.

A 16-months-old boy was admitted with increased tone in his limbs and brisk tendon reflexes. He had lost his motor skills from the age of 12 months when he was noticed to cease walking and after the age of 14 months he was no longer able to sit without support. He was born to healthy unrelated parents at term following a normal pregnancy. Birth weight was 3290 g. The neonatal period was normal. His early developmental milestones were normal; he sat unsupported at 6 months, pulled to stand at 9 months and walked holding on at 10 months. He began to speak at 12 months and progress of his mental development continued unimpaired. Except for a febrile illness with erythematous rash and vomiting at the age of 3 months he did not have any other illnesses.

Investigations at the age of 16 months were normal for blood count (leucocytes 9·6 × 10⁹/l, neutrophils 41%, lymphocytes 57%, monocytes 2%), liver function, urate, blood and urine amino and organic acids, blood lactate and pyruvate and lysosomal enzymes. Computed tomography of the brain and myelography showed no abnormality. The CSF contained 0·010 × 10⁶ white blood cells with 80% lymphocytes, 0·11 g/l protein and normal glucose. Enterovirus was isolated from the CSF.

The child had another febrile illness with a rash at 17 months and died at 20 months from fulminant Pseudomonas aeruginosa septicaemia with purulent cholecystis. At necropsy apart from cholecystitis the most important finding was in the CNS. The brain was normal in size and outward appearance but slight opacity of the meninges was noted. On coronal sectioning the only abnormality was slight enlargement of the lateral ventricles. Histological examination revealed slight to moderate lymphocytic infiltration of the cerebral and spinal meninges. Perivascular lymphocytic cuffs (fig A) were present in all regions of the cerebrum, brain stem, cerebellum and spinal cord. The infiltration was extensive but the individual cuffs were thin. In addition a moderate degree of microglial proliferation with nodule formation (fig B) was seen in the optic nerves, hypothalamus, thalamus, brain stem, cerebellum and spinal cord. Neuronal degeneration was less obvious in the cerebral and cerebellar hemispheres but more pronounced in the brain stem, where in addition to the colliculi nuclei pontis and...