Short report

A case of combined Pick's disease and Alzheimer's disease

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SUMMARY The diagnosis of combined Pick's and Alzheimer's disease is rare, and over the years different authors have used different criteria to arrive at such a diagnosis. A case is reported of presenile dementia in which the histological changes of Pick's disease and Alzheimer's disease were mingled. The brain showed no focal atrophy, but the Pick changes were most numerous in the hippocampus and in the temporal lobe. An antibody against the 155 kilodalton component of neurofilaments demonstrated not only neurofibrillary tangles and components of senile plaques, but also Pick's inclusions.

In the first half of this century Pick's disease was commonly diagnosed on gross morphological appearances alone; later the importance of the histological features was emphasised in conjunction with a lobar atrophy. The case reported here is one in which the unmistakable histological features of Pick's disease and Alzheimer's disease were present in a brain without focal atrophy.

Case report

HD, a caucasian male, was first seen at the age of 60 years when he gave a 4-year history of forgetfulness and of lack of concentration, leading to his early retirement from the Civil Service at the age of 58 years. Relatives had noted a change in his personality, being less outgoing than before.

In his past history a duodenal ulcer had been diagnosed at the age of 55 years and mild diabetes mellitus, responding to diet, two years later. On examination all of the tendon reflexes were brisk and his memory was very poor. He could not recall the names of four objects one minute later. No other abnormalities were noted in the central nervous system. Over the next 2 years he managed with the help of his wife, but when seen at 62 years of age, he had no spontaneous speech. Although he knew his address, he did not remember his age, and needed help with dressing and undressing. He was admitted to hospital aged 63 years for long-term care; the admission was precipitated by the development of grand-mal seizures. He remained in hospi-

tal for 3 years with a gradual deterioration in his condition and died aged 66. In hospital he continued to have occasional grand-mal fits (once in every few months) and developed severe apraxia. He also became aphasic and resorted to making a whining sound for communication. Neurological examination failed to reveal any other abnormal signs.

Post-mortem examination gave the immediate cause of death as bronchopneumonia, but no other abnormalities in organs outside the central nervous system were found. The brain weighed 1276 g with slight widening of the sulci particularly over the frontal lobes. The leptomeninges, large cerebral blood vessels and cranial nerves were normal. The brainstem and cerebellum displayed no abnormality. On coronal sectioning both lateral ventricles and the third ventricle were grossly dilated (the ventricular system holding 80 g of water), with extensive disruption of the septum pellucidum, but no obstructive lesion was seen. The bodies of the caudate nuclei appeared smaller than usual. The cortical ribbon was not obviously narrowed.

Histology revealed widespread neuritic plaques and neurofibrillary tangles in the hippocampus, and in all the lobes, of which the occipital were least affected. Granulovacuolar change was prominent in the pyramidal cells of the hippocampus, but was also seen in the neocortex, particularly in the temporal lobe. In addition to these changes ballooned neurons, many containing round argyrophilic inclusions and histologically resembling Pick cells and Pick bodies were present in the hippocampus and scattered throughout the neocortex (fig 1). There were no marked focal accumulations of these cells though they were most easily found in the temporal lobe and hippocampus. Congo red staining demonstrated the amyloid core of the neuritic plaques and also the presence of widespread congophilic angiopathy of the larger vessels in both the leptomeninges and the brain. Holzer preparation

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Fig 1 *Pick body in pyramidal cell layer of hippocampus with granulovacuolar change in adjacent neurons (Glees and Marsland, $\times 125$)*

showed not only astrocytic proliferation around plaques, but also a patchy gliosis of the subcortical white matter in the temporal lobe.

Electron microscopy of the cortex revealed the presence of intracellular accumulations of filaments having the characteristic morphology of the paired helical filaments of Alzheimer's disease, but cells containing Pick's inclusions were not included in this sample.

A monoclonal antibody, BF10, in use in this laboratory, was applied to a range of sections. Plaques and tangles were stained well, and the preparation, although resembling silver impregnation, gave a better definition of these structures. Moreover, Pick bodies also gave an unequivocally positive reaction to this antibody (fig 2), BF10 has been shown to be directed against the 155 kilodalton polypeptide component of neurofilaments and in its specific staining of tangles (fig 3), and components of neuritic plaques (fig 4), demonstrates that these abnormal structures share an antigen in common with neurofilaments.¹ Similarly, the staining of Pick bodies proves that neurofilament antigens are present in these

Fig 2 *Pick body in pyramidal cell layer of hippocampus (BF10 monoclonal antibody, $\times 200$)*

Fig 3 *Neurofibrillary tangles in pyramidal neurons of hippocampus (BF10 monoclonal antibody, $\times 125$)*

Fig 4 *Plaques in parahippocampal gyrus (BF10 monoclonal antibody, $\times 50$)*

inclusions, and thus provides immunological support for previous ultrastructural investigations.^{2,3}

Discussion

The definition of cases of combined Pick's and Alzheimer's disease presents considerable difficulty. Although Alzheimer later described the distinctive histological changes associated with circumscribed cerebral atrophy, Pick's original case report was confined to gross appearances only. There are two types of combined disease reported in the literature. In the first type the brains display focal atrophy, the atrophic areas showing marked loss of neurons with some cortical gliosis, but without distinctive histological changes, whilst the remainder of the brain is afflicted with florid Alzheimer changes. In the second group the gross appearance of Pick's disease (that is focal atrophy) is confirmed histologically

with the findings of ballooned neurons and Pick bodies within the atrophic lobe: profuse Alzheimer changes occur elsewhere in the cortex.

Combined cases of both the above mentioned types have been reported from the 1930s to the present time. Moyano⁴ described cases in which striking Alzheimer changes were found in brains with marked focal atrophy, although there was no histological evidence of Pick's disease. In contrast, Berlin⁵ reported two cases with marked temporal atrophy, in which areas there were Pick changes of ballooned cells with argyrophilic inclusions, whilst the remainder of the cortices contained numerous plaques and tangles. Some of the cytoplasmic structures appeared to be transitional forms between neurofibrillary degeneration and Pick's inclusions, suggesting that they may be phases of the same degenerative process. More recently examples of both of these types⁶⁻⁸ have been described, including one patient with Down's syndrome and dementia.⁸

Our case is unusual in a number of respects. First, although there was a history of dementing illness lasting 10 years, the brain weighing 1276 g was not markedly shrunken and showed no focal atrophy. Second, histology revealed widespread and diffuse Pick and Alzheimer changes, and third, granulovacuolar change occurred outside the hippocampus, a most unusual feature in Alzheimer's disease and possibly related to the simultaneous appearance of Pick changes in the brain.

The similarity of Pick's cells to cells undergoing central chromatolysis has been noted in both histological⁹ and ultrastructural studies.² Williams⁹ described ballooned neurons with an argyrophilic inclusion in a wide range of conditions, including tumours, syphilis and vascular disease and concluded that recent axonal damage close to the cell body may lead to Pick changes. An ultrastructural study of Pick's disease revealed that Pick bodies consisted of poorly demarcated accumulations of filaments, tubules, ribosomes and lipochrome and thus closely resembled the appearances of central chromatolysis. It was postulated that Pick changes could result from retrograde or trans-synaptic degeneration.²

In our case the combined histological features of Pick's and Alzheimer's disease could be explained by suggesting that primary Alzheimer degeneration of cortical and hippocampal neurons caused trans-synaptic degeneration of neurons receiving association or hippocampal commissural fibres from such degenerating cells, thus resulting in central chromatolysis, and therefore the appearance of

Pick's cells and combined disease. This clearly cannot explain those cases which show a marked lobar atrophy, unless the affected neurons have a special sensitivity to trans-synaptic degeneration. In a quantitative assessment of Pick inclusions the hl sector of the hippocampus was most severely affected.¹⁰

The problem of Pick and Alzheimer combined disease has always been a difficult and confusing one. Delay and Brion,¹¹ in reviewing the literature went so far as to say that only two convincing cases had been reported — those by Berlin.⁵ Their very rarity is a serious bar to investigation, and it seems probable that only a better aetiological understanding of the "pure" forms of Alzheimer's disease and Pick's disease will lead to an explanation for the occurrence of combined forms.

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