Short report

Subacute spongiform encephalopathy (Creutzfeldt-Jakob disease) with amyloid angiopathy

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SUMMARY A case is reported of Creutzfeldt-Jakob disease associated with amyloid infiltration of cerebral vessels. The duration of progressive dementia was only 4 months. Neuritic plaques were not a feature of the pathology. This report emphasises the association of spongiform encephalopathy with the presence of amyloid in the brain.

Amyloid deposition in the brain in Creutzfeldt-Jakob disease may be found in the form of round kuru-type plaques or in the core of neuritic plaques¹ which may be present incidentally. Involvement of cerebral blood vessels (amyloid angiopathy) is much less frequent,² although it is fairly common in other forms of dementia, particularly in Alzheimer's disease.³

We report the clinical and neuropathological findings in a patient with rapidly progressive dementia, in whom spongiform encephalopathy typical of Creutzfeldt-Jakob disease was associated with severe amyloid infiltration of cerebral blood vessels.

Clinical history

A 62-year-old research engineer was well until 2 months before admission to the Central Middlesex Hospital. He was unable to contribute to his own history. His wife stated that his intellect had deteriorated progressively, memory for recent events was poor, and he was confused. His balance deteriorated over the same two month period, with many falls. There had been no disturbances of consciousness. He was not taking any medication. His father was said to have had Parkinson's disease, but there was no other family history of neurological illness.

On examination, although alert he was disorientated,

knew his address but could not state his date of birth or occupation. Blood pressure was 160/110 mm Hg. There was mild bilateral papilloedema but no other cranial nerve abnormalities. Tone and power were normal. Co-ordination was impaired, particularly in the legs. Tendon reflexes were sluggish in the arms, absent in the legs, and the plantar responses were flexor. There were no frontal lobe signs. No abnormalities could be found on limited sensory examination. Gait was ataxic, and he had an unsteady stance even with his eyes open.

The following investigations gave normal results: full blood count, ESR, blood urea and electrolytes, liver function tests, blood calcium, random blood glucose, WR, B12 and folate, chest and skull radiographs, bilateral carotid and vertebral angiograms. The CSF was sterile, contained an occasional red blood cell, no white cells, protein 0.1 g/l; immunoglobulins were normal and the WR negative. An air encephalogram and CT scan were consistent with cerebral atrophy. An EEG performed 35 days before death showed constant and persistent irregular theta components over a wide area of the left cerebral hemisphere, maximal over the left anterior temporal region. A repeat EEG 4 weeks later showed a significant excess of slow components over the right hemisphere as well. There were no periodic complexes. There were no epileptogenic features.

Treatment with dexamethasone and amantadine did not produce any improvement. Within a month of admission he became bed-bound and mute; myoclonic jerks of all four limbs were observed in the terminal phase of his illness. Mild papilloedema persisted throughout. He died four and a half months from the onset of symptoms.

Neuropathological examination

Necropsy was carried out at the Central Middlesex Hospital, and the immediate cause of death was bronchopneumonia. Other abnormalities were confined to the

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Fig (a) Section of temporal cortex shows marked spongiform change, neuronal loss and a deposit of amyloid (arrow). H & E $\times 350$. (b) Section of cerebellum. Spongiform changes are present in the molecular layer. H & E $\times 350$. (c) Section of cortex stained with phosphotungstic acid—haematoxylin shows numerous astrocytes (arrows), spongiosis and an amyloid deposit (*). $\times 350$. (d) Section of occipital region shows infiltration by amyloid in the walls of small vessels within the cortex and in the overlying meninges. Congo red $\times 110$.

nervous system. Only the brain was available for neuropathological study. The unfixed brain weighed 1,420 g and the meninges were slightly thickened over the convexity. The blood vessels were free of atheroma but were more rigid than normal.

Coronal slices showed slight dilatation of the lateral and third ventricles, but the cortex, white matter, basal ganglia, brain stem and cerebellum did not show any macroscopic abnormality.

Blocks were taken from many regions of both cerebral hemispheres, brain stem and cerebellum. In addition to routine techniques, neurohistological methods used included Holzer's method for astrocytes and silver impregnation of axons. Microscopically status spongiosus (fig a) was present in some areas of grey matter while other regions were relatively spared. There was marked spongiform change affecting the full thickness of the cortex in all temporal lobe gyri, most severe in the parahippocampal gyrus where the vacuoles were large and, in places, coalescent. In the hippocampus itself there was marked status spongiosus of the pyramidal layer and end folium and many of the pyramidal cells contained granulo-vacuolar inclusions. Caudate, putamen, peri-aqueductal grey matter, colliculi of the midbrain and the molecular layer of the cerebellum (fig b) all showed a moderate degree of spongiform change composed of small discrete vacuoles. The tegmentum of pons and medulla were affected to a lesser degree. Marked neuronal loss and astrocytic hyperplasia (fig c) were found in the regions where spongiform changes were present and the severity of cell loss and gliosis paralleled the degree of status spongiosus. There was marked fibrous gliosis of the white matter throughout the cerebral and cerebellar hemispheres and some evidence of Purkinje cell degeneration.

Amyloid deposits ranging from 5 to 40 μ m in diameter were present in small numbers in the cortex (figs a and c) in the basal ganglia, brain stem and cerebellar molecular layer. Some of the deposits had peripheral radiating fibrils, similar to "kuru plaques", but most consisted of rounded amorphous bodies. The deposits had a strongly positive reaction with Congo red and PAS, and were not argyrophilic. They were not related to blood vessels. Occasional neuritic plaques were present in the temporal, parietal and occipital cortex. These were argyrophilic and some had central amyloid cores. A very few nerve cells with neurofibrillary tangle were present in frontal and temporal cortex.

Amyloid angiopathy (fig d) was widespread throughout the brain, involving both meningeal and cortical arterioles, and also small meningeal arteries and a few veins. The occipital regions were most severely affected. The vascular amyloid gave the typical staining reactions and greenish birefringence under polarised light after staining with Congo red. (No attempt was made to identify the type of amyloid present by immunocytochemistry). There were no areas of infarction or haemorrhage.

Discussion

The combination of spongiform change, astrocytic hyperplasia and nerve cell loss is characteristic of

Creutzfeldt-Jakob disease. The patchy uneven cortical distribution with heavy involvement of deep grey nuclei and inferior temporal cortex, may partly explain the absence of typical EEG appearances. Amyloid plaques of the kuru type may also be part of Creutzfeldt-Jakob disease pathology⁴ and are also seen in natural and experimental scrapie.^{5,6} Neuritic (senile) plaques have also been described in Creutzfeldt-Jakob disease mainly in patients whose age at death is significantly older than patients with Creutzfeldt-Jakob disease without plaques.¹ Both kuru and neuritic type plaques have been found in association with amyloid angiopathy⁷⁻¹⁰ and it is difficult to determine in this case whether the plaques of varying form are related to Creutzfeldt-Jakob disease or to amyloid angiopathy. Moreover, it is unclear whether all the pathological features, that is spongiform encephalopathy, plaques and amyloid angiopathy, are part of the same disease or represent co-existing diseases.

Amyloid angiopathy has been described in many forms of dementia^{3,7-9} but an association with spongiform encephalopathy is not so well recognised. We know of five other instances of this association.^{1,2,9,11,12} The age range of these ranged from 62 to 76 years and the duration of illness from 10 weeks to 5 years. Only one case was familial and suffered from a slowly progressive cerebellar ataxia with dementia, clinically quite different from the present case.

The time taken for the widespread amyloid deposition to develop in cerebral vessels is not known, but it has usually been described in conjunction with dementing illness of long duration. In the present case, symptoms started 4-5 months before death; two other cases with spongiform encephalopathy and amyloid angiopathy also had short histories. The case described by Hogenhuis *et al*¹² had an illness lasting 4 months, while in the case of Gaches *et al*¹¹ the duration of disease was only 2-3 months. It is possible that these patients suffered from primary cerebrovascular amyloidosis which preceded and may have predisposed to the development of spongiform encephalopathy. This could be due to a local effect, facilitating access to the brain by the infective agent. The known familial associations of Creutzfeldt-Jakob disease¹³ and of cerebral amyloid angiopathy,¹⁴ together with the occurrence of both conditions in the same family,² suggest a genetic factor shared by these diseases.

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