Limbic encephalitis occurring in association with Alzheimer's disease

R C Sutton, M H Lipper, H R Brashear

Abstract

Paraneoplastic limbic encephalitis is a rare cause of subacute dementia. A patient with limbic encephalitis and small-cell lung carcinoma is reported in whom the onset of subacute cognitive impairment was obscured by concurrent Alzheimer's disease. MRI revealed increased T2 signal in medial temporal lobes which corresponded to inflammatory pathology demonstrated at necropsy. High titres of antineuronal antibody (type II, anti-Hu) were present at death. Direct immunofluorescent staining of necropsy tissue revealed IgG bound to most remaining neurons in the temporal lobe. Antineuronal antibody screening and MRI are important in detecting limbic encephalitis.

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Limbic encephalitis was first described as a unique clinical and pathological syndrome by Brierly in 1960.¹ Its association with carcinoma was elucidated by Corsellis in 1968.² Subsequent reports have established limbic encephalitis as one of several classic clinico-pathological presentations of paraneoplastic disorders.³ Limbic encephalitis is characterised clinically by subacute cognitive deterioration with variable degrees of anxiety, confusion and memory impairment which may be difficult to differentiate from other causes of dementia. Laboratory and radiographic findings are usually non-specific. An exception is the finding of circulating antineuronal antibodies which point strongly to an underlying neoplasm.^{4,5} Since paraneoplastic limbic encephalitis and the associated malignancy are potentially treatable, it is important to differentiate this syndrome from other causes of cognitive impairment. We report the clinical, immunological, radiographic and pathological features of a case of limbic encephalitis occurring in association with Alzheimer's disease.

Case report

A 78 year old white woman began to have subtle memory and personality changes in 1987. She complained of dyspnoea in December 1987, and x ray and CT scan of the chest at another hospital suggested two left lobe nodules. Bronchoscopy and biopsy were negative. In April 1989, repeat CT scan

revealed hilar adenopathy, but bronchoscopy was again negative. In June 1989, she was evaluated for unsteady gait and numbness in her hands. A CT scan of the chest showed improvement. CSF was normal except for a protein of 122 mg/dl. CT and MRI scans of the head were unremarkable except for mild cortical atrophy. She became confused and incontinent and was transferred to the University of Virginia Health Sciences Centre.

On admission the patient was alert but confused, oriented only to person. She had severe memory and cognitive impairment. Cranial nerve examination was normal. Strength was 4/5 in all muscle groups with mild hypotonia. There was marked dysmetria. Sensory examination was inconsistent. Deep tendon reflexes were absent with bilateral Babinski responses. Chest x ray showed no masses. CSF was sterile with protein 70 mg/dl and 6 WBCs. EEG revealed bihemispheric slowing. An MRI scan of the head (fig 1) showed increased signal intensity involving the medial temporal lobes on T2-weighted images. The patient was treated

Figure 1 Axial T2-weighted (2500/90) MRI demonstrating diffuse increased signal intensity in the medial portions of both temporal lobes (arrows).

Departments of
Neurology and
Behavioral Medicine
and Psychiatry
University of Virginia
School of Medicine
Charlottesville,
Virginia, USA

Department of
Pathology, Division of
Neuropathology
R C Sutton

Department of
Radiology
M H Lipper

Department of
Neurology, and
Department of
Behavioral Medicine
and Psychiatry
H R Brashear

Correspondence to:
Dr Brashear, Department of
Neurology, Box 394,
University of Virginia Health
Sciences Center,
Charlottesville, VA, 22908,
USA

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Figure 2 Section of the amygdala demonstrating perivascular lymphocytic infiltrate within the meninges (hematoxylin and eosin, $\times 250$).

empirically with acyclovir. A brain biopsy of the right temporal lobe showed perivascular lymphocytic infiltrates in the leptomeninges. She deteriorated rapidly, became comatose and died on 22 August 1989.

PATHOLOGY

Necropsy revealed pulmonary emphysema with recent pulmonary emboli. A 2×2.5 cm small-cell carcinoma of the lung was present in the left hilum. A 5×9 cm adenocarcinoma of the colon was found.

The brain weighed 1290 grams and appeared grossly normal except for post surgical changes over the right temporal lobe. Microscopic examination revealed chronic perivascular inflammatory changes in the meninges (fig 2) and encephalitis with lymphocytic infiltrates of the medial temporal lobes. There was neuronal loss and gliosis in the olivary complex and ganglioradiculitis at multiple levels. There were recent small infarcts in the right amygdala, pontine tegmentum and left lateral basis pontis and old lacunar infarcts in the right globus pallidus. On Bielschowsky silver staining there were moderate numbers of neuritic plaques, greater than 15 per mm^2 in all areas of the neocortex, amygdaloid bodies and hippocampal formations, meeting neuropathological criteria for Alzheimer's disease.⁶ There were numerous neurofibrillary tangles and granulovacuolar degeneration in the hippocampi and modest numbers of cortical neurofibrillary tangles.

IMMUNOFLUORESCENCE

Indirect immunofluorescence was carried out with the patient's serum as described previously.⁷ Serum was titrated against normal human cerebellum using FITC-conjugated goat anti-human IgG as secondary. Screening produced intense, finely granular nuclear and cytoplasmic staining of all neurons (fig 3) and no other cells in a type II pattern⁸ (anti-Hu⁴). The endpoint titration was 1:1,280. Normal

Figure 3 Indirect immunofluorescence of normal human cerebellum incubated with 1:80 dilution of patient serum followed by FITC-conjugated anti-human IgG. There is intense, granular labelling of nuclei and cytoplasm of all neurons typical of type II (anti-Hu) staining ($\times 475$).

serum controls produced no staining.

Direct immunofluorescence was performed on frozen sections of the patient's necropsy tissue as described previously.⁹ Immunostaining produced moderate to intense cytoplasmic and nuclear labelling of most remaining neurons in temporal cortex indicating bound IgG (fig 4). Neurons in the cerebellum, brainstem and dorsal root ganglia

Figure 4 Direct immunofluorescence of patient's temporal cortex indicating bound IgG in most but not all neurons and no other cells ($\times 320$).

were also labelled but non-neuronal cell types were not stained. Direct immunofluorescence of normal brain produced no staining.

Discussion

Limbic encephalitis is a rare complication of cancer, most often small-cell lung carcinoma, but occasionally other lung tumours, Hodgkin's lymphoma, and other malignancies.³ Limbic encephalitis is one manifestation of a spectrum of paraneoplastic syndromes, including encephalomyelitis and sensory neuronopathy, associated with small-cell carcinoma. This group of paraneoplastic neurological syndromes is distinguished by the occurrence of circulating antineuronal antibodies which label nuclei and cytoplasm in a pan-neuronal (type II) pattern⁸ and are directed against neuronal antigens of 35–40 Kd molecular weight (anti-Hu).⁵

Paraneoplastic limbic encephalitis is usually characterised by subacute dementia. Alzheimer's disease, the most common cause of dementia, also has a predilection for limbic structures and usually presents with the insidious onset of similar symptoms. As illustrated by this patient, the gradual progression of a degenerative dementia can obscure the onset of limbic encephalitis. Subacute behavioural changes are not uncommon in patients with Alzheimer's disease, frequently due to medication effects, systemic illnesses or changes in environment. Memory impairment in both disorders compromises the patient's ability to give an accurate history. Routine laboratory and radiographic features usually show little or no abnormalities. Thus the initial clinical features of the onset of limbic encephalitis may be ignored or attributed to other causes.

Most cases of paraneoplastic limbic encephalitis were recorded before the advent of CT and MRI. The few reported cases indicate CT is insensitive in this condition as it is unremarkable or may show atrophy,^{10 11} although contrast enhancement may be seen.¹² MRI may show increased signal intensity on T2-weighted images in affected portions of the temporal lobes^{10 11 13} (fig 1). Our report correlates these MRI findings in necropsy confirmed limbic encephalitis with demonstrated antineuronal antibodies. Late in the course of limbic encephalitis MRI scans may show evidence of temporal lobe atrophy, such as parenchymal volume loss and dilatation of the temporal horns.^{10 12}

Routine laboratory studies are usually of little help in the diagnosis of limbic encephalitis.³ CSF protein may be elevated with occasional white cells. In contrast, the detection of anti-neuronal antibodies is highly specific for a paraneoplastic neurological disorder.⁵ Indirect immunofluorescence demonstrated high serum titres of antineuronal antibody in a type II pattern typical for both encephalomyelitis and ganglioradiculitis associated with small-cell carcinoma of the lung. The specificity and noninvasiveness of indirect immunostaining emphasise the importance of early consideration of limbic encephalitis.

Direct immunostaining of neuron-bound antibodies in affected areas of the CNS suggests a direct role for antineuronal antibody in the pathogenesis of paraneoplastic limbic encephalitis, but few such clear associations have been reported in the literature. Several authors^{4 14–18} have described neuronal immunostaining in patients with paraneoplastic disorders, but without precise correlation with clinical symptoms and pathology. Brashear *et al*⁸ demonstrated direct immunostaining of neurons in multiple regions, including temporal lobe structures in a patient with paraneoplastic encephalomyeloneuritis and prominent limbic encephalitis. Dalmau *et al*¹⁸ eluted antineuronal antibody with anti-Hu reactivity from post mortem brain tissue of five patients with paraneoplastic encephalomyelitis and limbic involvement. Our case confirms that antibody can be detected on target neurons in active limbic encephalitis and shows the utility of obtaining frozen tissue.

This report shows the extent to which cognitive impairment due to a progressive neurodegenerative disorder, such as Alzheimer's disease, can obscure the onset of a subacute dementia, in this case due to limbic encephalitis. Most laboratory tests do not narrow the differential diagnosis, however, MRI may demonstrate typical involvement of limbic structures. Antineuronal antibody screening can be diagnostic, indicating the presence of occult carcinoma responsible for the paraneoplastic disorder.

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