

SHORT REPORT

Chorea resulting from paraneoplastic striatal encephalitis

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Abstract

A 73 year old man presented with progressive choreic movement and dementia. An antineuronal antibody that recognised a 68 kDa band on a western blot was found in the patient's serum; this antibody immunolabelled neuronal somata in rat brain. Postmortem examination showed a small cell lung cancer and severe neuronal loss with lymphocytic infiltration in the striatum that was more severe in the caudate head. This is thought to be the first pathologically proved case of paraneoplastic chorea with striatal encephalitis.

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The discovery of antibodies against onconeural proteins in the serum and CSF of patients with malignancy and paraneoplastic syndromes has shown the existence of immune responses against the tumour and the nervous system. Some syndromes have been accepted as paraneoplastic disorders because of their frequent association with a specific tumour type, and selective involvement of the nervous system with corresponding major symptoms and signs.¹ However, chorea as a remote effect of malignancy is exceedingly rare, and the lesions that cause chorea have yet to be established. We have recently encountered a patient who manifested chorea as an initial and cardinal symptom, and in whom postmortem examination showed small cell lung cancer and inflammatory lesions that were almost restricted to the basal ganglia of the brain. To our knowledge, this is the first postmortem established case of chorea resulting from paraneoplastic striatal encephalitis.

Case report

CLINICAL COURSE

A 73 year old Japanese man was admitted to our hospital on 2 June 1997 complaining of restlessness. He was not demented at the time of the initial examination, but his mood was manic. On neurological examination, he showed choreic movement in his limbs. No cranial nerve signs were evident. All deep tendon reflexes were diminished. Neither muscle weakness nor sensory disturbance was seen and

the Romberg test gave a negative result. The patient walked unsteadily, displaying chorea. The laboratory tests showed no significant findings except a slight increase in concentrations of C-reactive protein, creatine kinase, and lactate dehydrogenase; thyroid function was normal. A chest radiograph showed swelling of the left hilar lymph nodes. Magnetic resonance imaging of the brain demonstrated low signal intensity on T1 weighted images and high signal intensity on T2 weighted images of the bilateral caudate nucleus (fig 1).

The patient was treated with lithium carbonate and clonazepam, which was not beneficial. His choreic movements became generalised and worsened. The purposeless involuntary movements, which were less rapid than myoclonus in character, involved the arms, legs, trunk, and neck, and were present all day and absent during sleep. They were identical with the eyes closed or open. On 12 June, the patient's verbal intelligence quotient (IQ) score was 76 (a performance IQ test was not performed). His mental function deteriorated and the choreic movements progressed rapidly; he fell often and bruised his head. On 20 June, he became unable to walk, and could not understand complicated orders. An EEG showed diffuse slowing without any difference between the right and left hemispheres. No periodic synchronous discharges were seen. A chest radiograph disclosed a small mass lesion on his left bronchus. Somatosensory evoked potentials were not examined, nor was a nerve conduction study performed. On 6 August, his CSF showed normal glucose and protein content with 1.3 lymphocytes/mm³ and negative cytology.

For screening for antineuronal antibody, western blot analysis was performed, using the cerebral grey and white matter, sciatic nerve, liver, and kidney obtained from a man who died of a non-neurological disorder, as well as the cerebrum, cerebellum, liver, and kidney dissected from a mouse killed under anesthetic. Each sample was homogenised in Tris buffered saline (TBS) containing 1 mM EDTA, 1 mM phenyl methyl sulfonyl fluoride, and 0.32 M sucrose. It was then centrifuged, and the supernatants were boiled in modified Laemmli's sample buffer. Fifty micrograms of each preparation were loaded for electrophoresis on 10% SDS-polyacrylamide slab gel, and trans-

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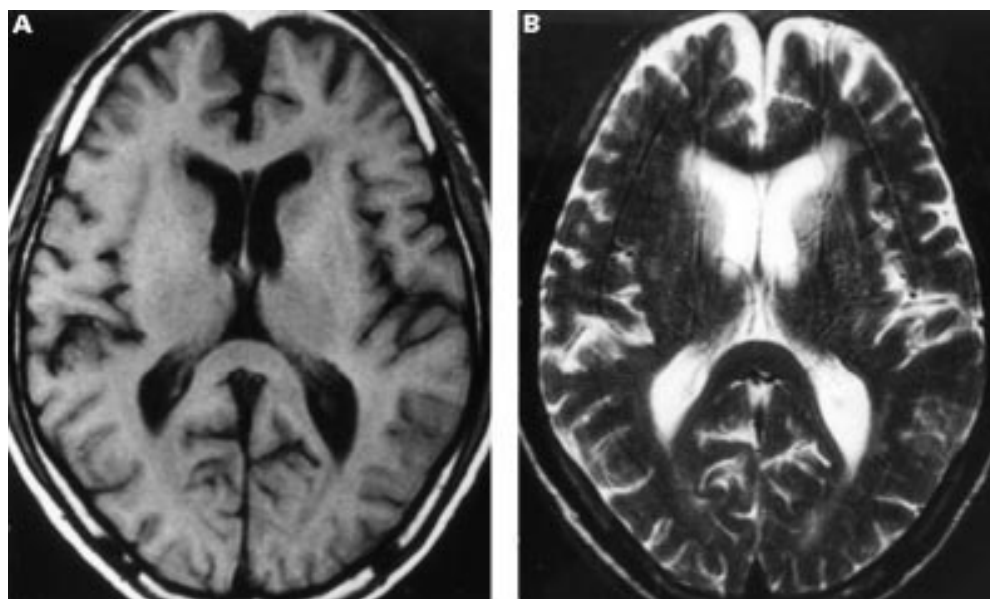


Figure 1 Magnetic resonance image through the basal ganglia. Reduced intensity is evident in the T1 weighted image of the bilateral caudate head (A), and markedly increased intensity is evident in the T2 weighted image (B).

ferred to nitrocellulose paper electrophoretically. The blotted papers were incubated at room temperature first with TBS containing 3% skimmed milk (TBSM), and then, in the following sequence, with a particular patient's serum diluted at 1:200 in TBSM, biotinylated anti-human IgG (γ -chain specific; Vector, Burlingame, CA, USA; diluted 1:1000), then avidin-biotin peroxidase complex (ABC reagent; Vector). Each incubation required 1 hour, which was followed by rinsing with TBS. The blots were finally incubated with 4-chloro-1-naphthol (Sigma, St Louis, MO, USA) and hydrogen peroxide for the colour development. The results showed that the serum of this patient contained an antibody that recognised a 68 kDa band only on a western blot of the homogenates of human cerebral grey and white matter, and murine cerebrum and cerebellum (fig 2). Anti-Hu, anti-Yo, and anti-Ri antibodies were not detected in the serum by enzyme linked immunosorbent assay. Cryostat sections of the rat brain, liver, and kidney after fixing in 4% paraformaldehyde were submitted for immunohistochemical examination using the patient's serum (diluted 1:1600) and CSF (diluted 1:5). Positive staining was found in neuronal cell bodies and proximal dendrites, being more pronounced in the thalamus and hippocampus (data not shown), but not in the liver or kidney. The control serum from 20 healthy volunteers, 35 patients with various types of spinocerebellar degeneration, and two patients with Huntington's disease did not react with any tissue samples.

As paraneoplastic encephalitis was strongly suspected, the patient was treated with intramuscular injections of dexamethasone for 77 days. Dexamethasone (initial dose 16 mg/day) was tapered; this improved his mental status only slightly. He died of bacterial colitis and pneumonia on 22 September, 3 months after the onset of his condition.

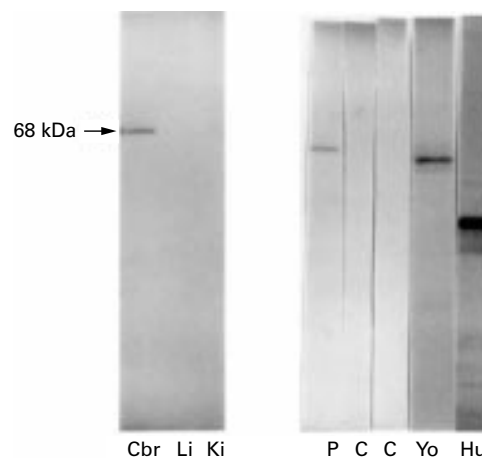


Figure 2 Western blot with the patient's serum (diluted 1:200), using murine cerebrum (Cbr), liver (Li), and kidney (Ki) homogenates, shows a 68 kDa band only on the cerebrum homogenate. In addition to serum (diluted 1:200) from the present patient (P), serum (diluted 1:200) from two healthy controls (C), an anti-Yo positive patient (Yo) and an anti-Hu positive patient (Hu) were also blotted as negative and positive controls (P and C, murine cerebrum homogenates; Yo and Hu, murine cerebellum homogenates).

POSTMORTEM EXAMINATION

At necropsy, small cell carcinoma in the upper lobe of the left lung was confirmed. Metastasis was found only in the left hilar lymph nodes. The above mentioned serum and CSF of this patient did not react with the tumour. The brain weighed 1200 g. Coronal sections of the cerebrum were examined; marked atrophy with brownish discoloration of the bilateral caudate nucleus was evident (fig 3 A). Histologically, the caudate nucleus exhibited severe neuronal loss with perivascular lymphocytic cuffing and proliferation of astrocytes (fig 3 B). The inflammatory reaction consisted of both B and T cells. Similar, but mild changes were seen in the anterodorsal portion of the putamen and the globus pallidus. The thalamus and subtha-

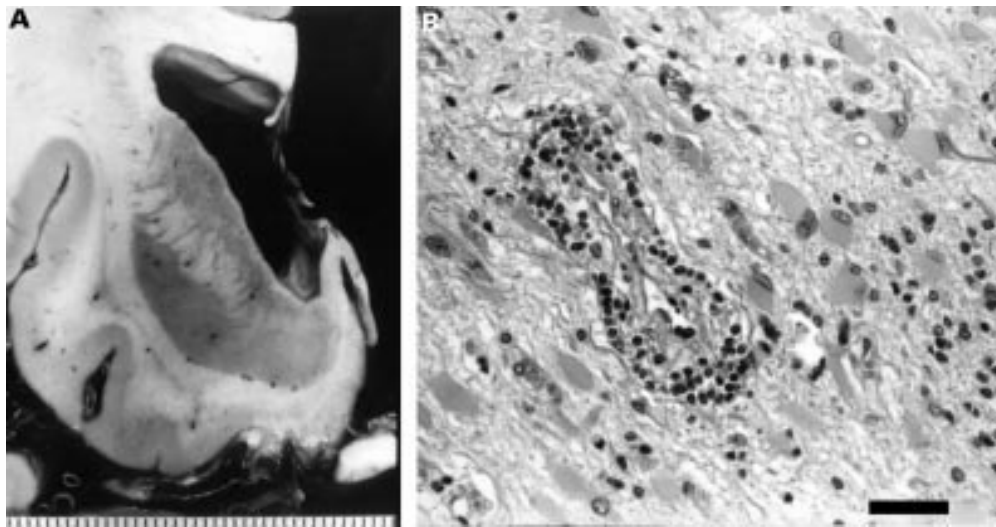


Figure 3 (A) Severe atrophy of the caudate nucleus is evident, mimicking Huntington's disease. (B) The caudate head exhibits marked neuronal loss, perivascular lymphocytic cuffing, and proliferation of astrocytes. Haematoxylin and eosin. Bar=30 μ m.

lamic nucleus were well preserved. In the cerebellum, mild loss of granule cells was noted, but the Purkinje cells were preserved. The midbrain, pons, and medulla oblongata showed no obvious abnormalities. In the spinal cord, posterior fascicles showed only slight myelin pallor with a few macrophages. The dorsal root ganglia showed mild neuronal degeneration with slight inflammatory infiltrates and several Nageotte nodules. The cerebral cortex showed no remarkable changes, apart from some senile plaques.

Discussion

The presence of a small cell carcinoma of the lung, the detection of an antineuronal antibody in the serum and CSF, and the neuropathology of the inflammatory reaction in our patient led to the diagnosis of paraneoplastic encephalitis that had affected primarily the basal ganglia.

Paraneoplastic encephalomyelitis is characterised clinically by a subacute, progressive course over weeks to months. The underlying malignancy is usually small cell lung cancer, and anti-Hu antibody is often detected. Although the distribution of the lesions throughout the central and peripheral nervous systems varies, so do the symptoms. The predominant regions of pathology have led to the characterisation of the following clinicopathological entities: limbic encephalitis, brainstem encephalitis, myelitis, ganglioradiculoneuritis, and autonomic neuropathy. However, selective involvement of the basal ganglia in paraneoplastic syndromes is exceedingly rare.

To our knowledge, only three patients presenting with chorea as a paraneoplastic symptom have been reported previously.²⁻⁴ Albin *et al*² reported the first case of chorea as a remote effect of small cell lung cancer. This patient showed a progressive multifocal neurological disorder with dystonia, ataxia, sensory neuropathy, and cranial nerve palsies in addition to chorea, and postmortem examination showed neuronal loss in the 10th and 12th cranial nerve nuclei, cerebellar cortex, and

posterior column, but not in the basal ganglia. Heckmann *et al*³ reported on a patient with chorea, ataxia, and sensory neuropathy in association with small cell lung cancer and anti-Hu antibody. Batchelor *et al*⁴ reported on a patient presenting with chorea and cerebellar ataxia as a remote effect of Hodgkin's disease, in whom anti-Hu and anti-Yo antibodies were negative, but immunohistochemistry using the patient's serum showed positive staining in the molecular layer of the cerebellum. Brain MRI of the patients demonstrated atrophy of the caudate nucleus on the T1 weighted image³ and increased signal intensity in the caudate head and anterior putamen on the proton weighted image.⁴ Unfortunately no postmortem findings were included in these two reports. Postmortem examination in our patient showed severe neuronal loss with lymphocytic infiltration in the striatum that was more severe in the caudate head. It has been established that the choreoathetosis seen in Huntington's disease is the result of a loss of the striatal neurons that project to the lateral segment of the globus pallidus.⁵ The lesion responsible for the chorea in the paraneoplastic syndrome seen in our patient was considered to be in the basal ganglia or, more precisely, the caudate nucleus.

The serum and CSF in our patient contained an antibody other than anti-Hu, anti-Yo, or others, as previously reported to occur in relation to paraneoplastic neurological syndrome.¹ Initially, paraneoplastic autoantibodies themselves were considered to be pathogenic. However, treatments that reduce antibody titres proved to be ineffective.⁶ In animal models, passive transfer of autoantibody or lymphocytes from patients with paraneoplastic disease, or passive transfer of lymphocytes sensitised to recombinant Yo protein antigen, has failed to induce the disease.⁷ Although the significance of the antibody found in our patient remains unclear, the neuropathological features of prominent lymphocytic infiltration with neuronal loss suggests the presence of

lymphocyte mediated neuronal cell death. Some recent studies have reported the possibility that cytotoxic T cells have roles in the pathogenesis of paraneoplastic neurological syndromes.⁸⁻¹¹

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