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Limbic encephalitis and small cell lung cancer
Clinical and immunological features

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Summary
*Paraneoplastic limbic encephalitis (LE) is considered a particular manifestation of paraneoplastic encephalomyelitis (PEM), a remote effect of cancer almost always associated with anti-neuronal antibodies (anti-Hu; also called ANNA 1) and small cell lung carcinoma (SCLC). In order to define the frequency of anti-Hu antibodies in LE with SCLC and to analyse possible clinical differences between patients with and without anti-Hu antibodies, the charts of 16 patients with LE and SCLC were reviewed. Eight patients (50%) had anti-Hu antibodies (anti-Hu+) whereas eight patients (50%) had no detectable anti-neuronal antibodies (anti-Hu–). The clinical and laboratory features of LE and time to diagnosis of SCLC were similar in the anti-Hu+ and anti-Hu– groups. Involvement of other areas of the nervous system compatible with the diagnosis of PEM was observed in seven (87.5%) patients of the anti-Hu+ group but in only one (12.5%) of the anti-Hu– group (*P *= 0.012). Five patients, including four of the anti-Hu– group, had a partial improvement of the LE after treatment of the SCLC. Another anti-Hu– patient improved spontaneously. Six patients of the anti-Hu+ group died from the neurological disorder, whereas in the anti-Hu– group the cause of death was progression of the SCLC in the three patients who died. The results of this study indicate that the absence of anti-Hu antibodies does not rule out the presence of an underlying SCLC in patients with a clinical diagnosis of LE. Patients with LE and SCLC who are without anti-Hu antibodies are less likely to develop PEM and seem to improve more often after treatment of the cancer than those who present anti-Hu antibodies.*

Keywords: limbic encephalitis, paraneoplastic encephalomyelitis, small cell lung cancer; anti-Hu antibodies

Abbreviations: LE = limbic encephalitis; PEM = paraneoplastic encephalomyelitis; SCLC = small cell lung carcinoma; anti-Hu+ = anti-neuronal antibodies present; anti-Hu– = anti-neuronal antibodies absent

Introduction
Limbic encephalitis (LE) is a neurological paraneoplastic syndrome or 'remote effect of cancer' usually associated with small-cell lung cancer (SCLC) (Brierley *et al*., 1960; Corsellis *et al*., 1968). LE is clinically characterized by subacute cognitive dysfunction with severe memory impairment, seizures, and psychiatric features including depression, anxiety and hallucinations (Bakheit *et al*., 1990; Newman *et al*., 1990). The EEG usually reveals focal involvement of one or both temporal lobes and the typical lesions on MRI consist of increased signal on T_2-weighted images or atrophy on T_1-weighted sequences in the medial aspects of one or both temporal lobes (Kohler *et al*., 1988; Dirr *et al*., 1990). The CSF examination may show mild lymphocytic pleiocytosis. Neuropathological studies reveal neuronal loss, perivascular inflammatory infiltrates and microglial nodules in the limbic structures especially the Ammon horn and amygdala (Brierley *et al*., 1960; Newman *et al*., 1990).

LE may present as an isolated neurological syndrome, or as part of a wider neurological disorder called paraneoplastic encephalomyelitis (PEM) which includes involvement of other areas in the central (cerebellum, brainstem, spinal cord) and peripheral (dorsal root ganglia) nervous system (Dorfman and Forno, 1972; Henson and Urich, 1982).

The clinical diagnosis of LE is difficult. In recent years, an anti-neuronal antibody that recognizes a family of RNA-

binding proteins expressed in the nervous system and SCLC, called anti-Hu (or ANNA 1), has proved useful in the diagnosis of patients with PEM associated with SCLC (Graus *et al*., 1986; Dalmau *et al*., 1992). Although limbic encephalitis is considered a particular manifestation of PEM, we and others (Antoine *et al*., 1992) have observed that occasional patients with LE and SCLC did not harbour anti-Hu antibodies. This observation prompted us to review the clinical and immunological findings of 16 patients with LE and SCLC to ascertain the frequency of anti-Hu antibodies and to analyse possible clinical differences between patients with and without anti-Hu antibodies.

Methods

We reviewed clinical and laboratory information retrospectively from patients with LE and SCLC, diagnosed between 1987 and 1994. Patients were identified from a database of 3500 patients who had been subjects in a study of anti-neuronal antibodies in serum, in the context of a suspected neurological paraneoplastic syndrome.

The diagnosis of LE associated with SCLC was given for any patient who fulfilled the three following criteria: (i) a clinical picture of seizures, memory loss or psychiatric symptoms suggesting involvement of the temporal lobes or the limbic system; (ii) a temporal relationship between neurological symptoms and the diagnosis of SCLC; (iii) absence of metastatic, metabolic, infectious, vascular or treatment-related causes that could account for the neurological dysfunction (these possibilities were ruled out by the clinical history, physical examination, CT or MRI of the head and appropriate analysis of blood and CSF). No patient had received cranial radiotherapy or chemotherapy before the onset of the neurological symptoms. In addition, patients had to present with at least one of the three following criteria: (i) an abnormal MRI characterized by a high intensity signal on T_2-weighted or atrophy on T_1-weighted images in one or both medial temporal lobes; (ii) lymphocytic pleocytosis in the CSF; or (iii) an EEG showing unilateral or bilateral temporal slow waves or sharp wave activity.

Anti-Hu antibodies were determined using immunohistochemical techniques and confirmed by immunoblot (Graus *et al*., 1986; Dalmau *et al*., 1990). Clinical information was concealed from the investigators involved in the laboratory studies.

Immunohistochemistry

Frozen sections of normal human frontal cortex were fixed with acetone for 10 min at 4°C. After inhibition of endogenous peroxidase with 0.3% hydrogen peroxide in PBS (phosphate buffered saline) for 5 min, sections were sequentially incubated in 10% normal goat serum for 20 min, the patient's serum (screening dilution 1 : 500) overnight at 4°C, biotinylated goat anti-human IgG, diluted 1 : 2000 for 1 h, and then the Vectastain avidin–biotin–peroxidase complex (Vector) for 30 min. The reaction was developed with 0.05% diaminobenzidine tetrahydrochloride (Sigma), 0.5% Triton X-100 and 0.01% hydrogen peroxyde in PBS. Predominant staining of the neuronal nuclei was considered suggestive of anti-Hu antibody immunoreactivity.

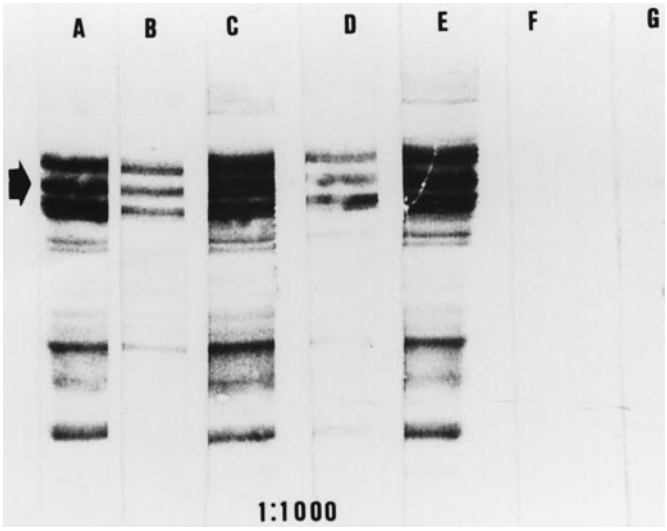

Fig. 1 Immunoblots of human neuronal nuclei probed with serum from patients with limbic encephalitis with (lanes A–E), and without (lanes F and G), anti-Hu antibodies. Positive sera recognize a set of three bands between 35 and 40 kDa (arrow).

Immunoblot

Purified human neuronal nuclei were separated by electrophoresis in a 12% sodium dodecyl sulphate–polyacrilamide gel and transferred to nitrocellulose. After blocking with 5% dry Carnation milk and 10% normal goat serum, strips were incubated with the patient's serum, diluted 1 : 1000 in 10% normal goat serum for 12 h, washed with PBS, and the avidin–biotin–peroxydase complex as described for the immunohistochemistry. The diagnosis of anti-Hu antibodies was made when the serum immunoreacted with three closely associated band of 35–40 kD (Fig. 1).

Results

A total of 16 patients with both LE and SCLC were identified. Eight patients (one female, seven male, aged 50–63 years) had high titres (>1 : 1000) of anti-Hu antibodies (anti-Hu+ group) and eight patients (one female, seven male, aged 47–68 years) did not harbour anti-Hu antibodies (anti-Hu– group).

The diagnosis of SCLC was confirmed by histology in 13 patients (five out of eight anti-Hu+ and eight out of eight anti-Hu– patients). In two anti-Hu+ patients, the SCLC could not be confirmed by histology or cytology, but both patients presented lung masses with large mediastinal lymph nodes compatible with lung cancer and the positive anti-Hu antibodies further suggested the diagnosis of SCLC (Dalmau

Table 1 *Occurrence of clinical and laboratory features in LE patients with and without anti-Hu antibodies*

	Anti-Hu+ patients (n = 8)	Anti-Hu– patients (n = 8)
Symptoms of limbic encephalitis		
Space and time disorientation	7	8
Memory deficit*	7	8
Dementia	4†	0
Seizures	5	7
Psychiatric disorders	7	7
Hallucinations	1	1
Signs of multifocal involvement of the nervous system	7	1
CSF findings		
Normal	1	0
Elevated protein (median, mg/l)	6 (76)	7 (49)
Pleiocytosis (median, WBC/mm^3)	6 (17)	6 (17)
Oligoclonal bands	5/6	1/2
MRI		
Normal	2/6	2/8
Increased signal on T_2-WI‡	4/6	6/8
Decreased signal on T_1-WI‡	0/6	2/8
Enhancement on CT‡	0/6	1/8
Temporal atrophy	1/6	1/8

WBC = white blood cells; WI = weighted image. *Thirteen patients (five anti-Hu+, eight anti-Hu–) had a Korsakoff syndrome. †The dementia was observed only late in the course in two out of four anti-Hu+ patients. ‡In temporal lobes.

et al., 1992). In another anti-Hu+ patient, the skin biopsy revealed metastasis from a small cell cancer but the primary tumour was never found.

LE preceded the discovery of the tumour in 13 patients (six out of eight anti-Hu+ and seven out of eight anti-Hu–). In the other three patients, the SCLC was diagnosed at the same time or 1 month before the onset of the LE. The median time between the first LE symptom and the radiological detection of the SCLC was 8 months (range from –1 to 24 months) in the anti-Hu+ group and 4.5 months (range 0–19 months) in the anti-Hu– group. All patients had the tumour confined to the chest at the time of diagnosis, except for one patient in each group.

Symptoms of LE developed in days or weeks, reaching a nadir in <3 months in 13 patients. Fifteen patients presented with symptoms well described in LE (*see* Table 1) such as confusion (15 patients), memory loss typical of Korsakoff syndrome (13 patients) and seizures (12 patients). Fourteen patients also had psychiatric symptoms of depression, anxiety, personality changes or hallucinations. One anti-Hu+ patient had only temporal and generalized seizures (which antedated the diagnosis of SCLC by 13 months) without other evidence of neurological dysfunction throughout the entire clinical course. In this patient CSF examination revealed 7 lymphocytes/mm^3 and the MRI of the head showed a high-signal lesion in the right medial temporal lobe on T_2-weighted images that did not enhance after gadolinium administration (Fig. 2). The patient died from progression of the SCLC 28 months after the first seizure. A neurological examination performed 1 month before death was normal.

Although LE was the most prominent neurological dysfunction in all the patients, signs of involvement at other levels of the neuraxis compatible with the diagnosis of PEM, were observed in seven out of eight of the anti-Hu+ patients but in only one anti-Hu– patient (P = 0.012). The median time between the onset of LE and symptoms of dysfunction of other areas of the nervous system was 1 month (range from −5 to 18 months). Two patients had a subacute sensory neuronopathy and three had areflexia or mild distal sensory signs. Five patients developed brainstem or cerebellar symptoms. The autonomic nervous system was affected in one patient with orthostatic hypotension, abnormal pupillary reflexes and urinary incontinence. The only anti-Hu– patient who had a multifocal involvement developed a sensory neuronopathy 4 months after the diagnosis of LE.

The CSF examination showed lymphocytic pleiocytosis in 12 patients (six in each group). EEG was performed for all the patients; it was normal in only one patient (anti-Hu–). In the other 15, the EEG showed sharp wave activity and epileptiform discharges in one or both temporal lobes (eight patients) or generalized slow waves. CT scans of the head were carried out for 15 patients; it was abnormal in only one patient (anti-Hu–), showing a noncontrast enhancing lesion in one temporal lobe. The MRI was abnormal in four out of six anti-Hu+ and six out of eight anti-Hu– patients. The most common abnormality was a high signal in the medial aspect of one or both temporal lobes on T_2-weighted images. In two patients, the MRI, carried out 10 and 18 months after the onset of LE, revealed only medial and anterior temporal lobe atrophy on T_1-weighted sequences.

Six patients (five anti-Hu+; one anti-Hu–) received several immunosuppressor therapies including immunoglobulins

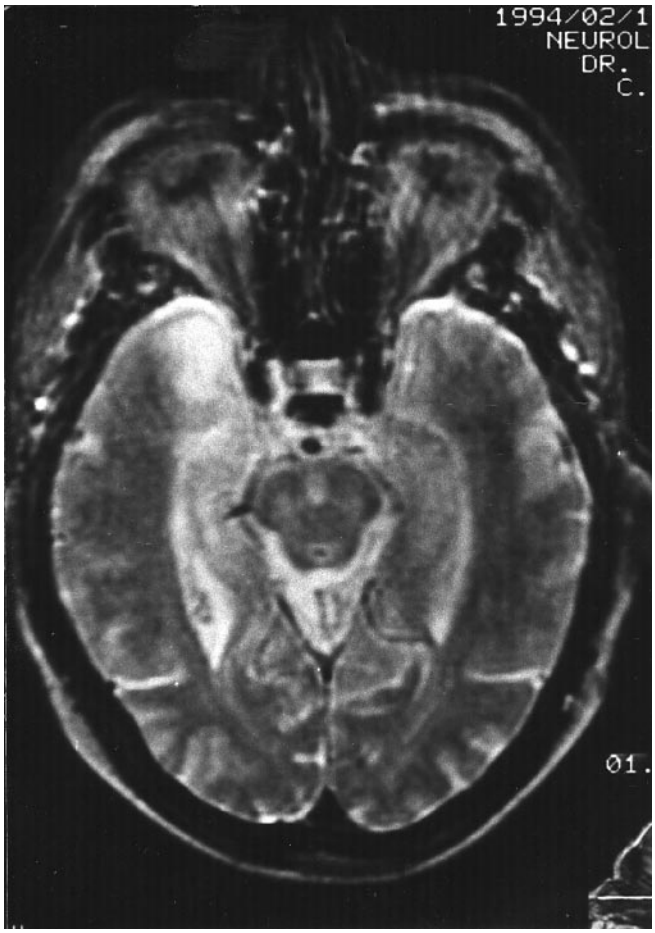

Fig. 2 T_2-weighted MRI showing high intensity signal in the medial and anterior right temporal lobe.

(three patients), plasmapheresis with cyclophosphamide (two patients) and corticosteroids (one patient), without improvement of the LE. Eleven patients (four anti-Hu+; seven anti-Hu–) received antineoplastic treatment (two of them also received immunosuppressors) and the SCLC had at least a partial response in all of them. Partial improvement of the LE after treatment of the SCLC was observed in one out of four anti-Hu+ patients and in four out of seven anti-Hu– patients. The improvement was in the state of confusion in all patients and, more rarely, in memory loss (one anti-Hu+; two anti-Hu–), and psychiatric symptoms (two anti-Hu–). This improvement was documented by serial neuropshychological tests in two anti-Hu– patients. Finally, LE improved spontaneously in one anti-Hu– patient.

Median follow-up was 18.5 months (range, 2–40 months) in the anti-Hu+ group and 18 months (range, 9–42 months) in the anti-Hu– group. All anti-Hu+ and three out of eight anti-Hu– patients died. In the anti-Hu+ group, six out of eight patients died from complications of their neurological disease, whereas in the anti-Hu– group, death was due to progression of the SCLC in the three patients who died.

A post-mortem study was performed in one anti-Hu+ patient who developed a cerebellar syndrome as well as the LE, and in one anti-Hu– patient with isolated LE at 40 and 13 months after the onset of the LE, respectively. On microscopic examination, there was severe neuronal loss and microglial nodules without inflammatory infiltrates in the hippocampus and amygdala in both cases. The anti-Hu+ patient also had neuronal loss and gliosis in the inferior olivary nucleus, and the dentate nuclei, and loss of fibres in the dorsal columns of the spinal cord. In contrast, the brainstem, cerebellum, spinal cord and dorsal root ganglia of the anti-Hu– patient were normal.

Discussion

The present investigation represents the largest reported study on paraneoplastic LE. Although we do not have pathological confirmation in most of our patients, the combination of the clinical picture, involvement of the temporal lobes as shown by MRI or EEG, the coincidence with SCLC and exclusion of other causes, combined, make the diagnosis of LE very likely. In two patients, histological diagnosis of the lung tumour was not obtained but the diagnosis of SCLC was assumed on the basis of X-ray findings and positive anti-Hu antibodies (Dalmau *et al*., 1992).

LE may be occasionally associated with thymoma (Ingenito *et al*., 1990; Antoine *et al*., 1995), testicular (Burton *et al*., 1988; Ahern *et al*., 1994), bladder (Case Records of the Massachusetts General Hospital, 1985), colon (Tsukamoto *et al*., 1993) or kidney (Dubas *et al*., 1982) cancer, or with Hodgkin's disease (Duyckaerts *et al*., 1985) but SCLC is by far the most frequent underlying tumour. Although anti-Hu antibodies are considered a marker for the neurological paraneoplastic syndromes associated with SCLC (Dalmau *et al*., 1992), the frequency of anti-Hu antibodies varies among the different paraneoplastic syndromes. Positive anti-Hu antibodies are routinely found in patients with PEM, paraneoplastic sensory neuronopathy or chronic intestinal pseudoobstruction (Lennon *et al*., 1991; Dalmau *et al*., 1992). On the other hand, only a few patients with SCLC and paraneoplastic opsoclonus myoclonus syndrome or isolated paraneoplastic cerebellar degeneration harbour anti-Hu antibodies (Hersh *et al*., 1994; Valldeoriola *et al*., 1994).

In the present study only 50% of the patients with LE had anti-Hu antibodies. No antibodies, other than anti-Hu, have been consistently reported in LE associated with SCLC. Sakai *et al*. (1994) described a neuronal antibody in a patient with LE and SCLC that recognized a neuronal RNA-binding protein that they called ple21. However, ple21 was found highly homologous with HuD and particularly HuC, two different but related proteins recognized by anti-Hu antibodies (Szabo *et al*., 1991; Manley *et al*., 1995). The clinical and radiological features of LE did not differ between anti-Hu+ and anti-Hu– patients. One anti-Hu+ patient presented with seizures, CSF pleocytosis and an abnormal MRI, but he did not develop the other neurological or psychiatric manifestations described in LE. This clinical expression of LE has not been reported previously. LE is characterized by a subacute and severe neurological disorder, but some patients

present seizures or psychiatric symptoms for several months before the full-blown syndrome of LE appears (Corsellis *et al*., 1968; Richardson *et al*., 1985; Franck *et al*., 1987). This patient's disease profile emphasizes the relevance of anti-Hu antibodies in the identification of indolent or unusual presentations of neurological paraneoplastic syndromes associated with SCLC (Graus *et al*., 1994).

An important feature of our study is that LE in anti-Hu– patients is more likely to remain isolated throughout the clinical course, whereas patients with anti-Hu antibodies usually develop a multifocal disorder compatible with PEM. This clinical observation was confirmed in the post-mortem analysis of the nervous system of the two LE patients with and without anti-Hu antibodies. The association between the presence of anti-Hu antibodies and a clinical picture of PEM is in agreement with the previous finding of Dalmau *et al*. (1992) who found multifocal involvement of the CNS in 73% of 15 patients with LE and anti-Hu antibodies. A correlation between isolated LE and negative anti-Hu antibodies has also been observed in patients with paraneoplastic cerebellar degeneration and SCLC (Dalmau *et al*., 1992; Valldeoriola *et al*., 1994). Patients with SCLC and an isolated paraneoplastic cerebellar syndrome throughout the entire clinical evolution of the disease are less likely to harbour anti-Hu antibodies. Some authors consider LE a particular manifestation of PEM (Henson and Urich, 1982; Dalmau *et al*., 1992), but the confirmation of this hypothesis must await the discovery of the pathophysiological mechanism of both syndromes. The possibility of a viral infection as the cause of LE has been frequently suggested on the basis of the neuropathological features, but it has never been demonstrated (Kaplan and Itabashi, 1974). The absence of anti-Hu antibodies in most patients with isolated LE and SCLC does not rule out the possibility that isolated LE may be an autoimmune disorder, but it does suggest that the immune mechanisms are not mediated through Hu-related antigens.

Unlike patients with PEM and anti-Hu antibodies that usually do not improve after anti-neoplastic or immunosuppressor therapies (Dalmau *et al*., 1992), a few patients with isolated LE improve after antineoplastic treatment with (Fishman *et al*., 1991) or without immunosuppressors (Brennan and Craddock, 1983; Richardson *et al*., 1985; Burton *et al*., 1988; Kaniecki and Morris, 1993). In the present study we confirmed this observation. Four (50%) patients without anti-Hu antibodies partially improved, whereas only one (12%) anti-Hu+ patient did so. Although the spontaneous improvment of one of our patients suggests caution at the time of evaluating the impact of a given therapy, we believe that early treatment of the tumour offers the best chances for improvement in patients with LE, particularly those without anti-Hu anibodies.

In conclusion, our study shows that in patients with a clinical diagnosis of LE, the absence of anti-Hu antibodies does not rule out the presence of an underlying SCLC. Patients with LE and SCLC who are without anti-Hu antibodies are more likely to improve after treatment of the tumour and have lower chances of developing PEM than those with anti-Hu antibodies.

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