Brain (1997), **120,** 1279–1300

Small-cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert–Eaton myasthenic syndrome

W. P. Mason,[1] F. Graus,[4] B. Lang,[5] J. Honnorat,[6] J.-Y. Delattre,[7] F. Valldeoriola,[4] J. C. Antoine,[8] M. K. Rosenblum,[2] M. R. Rosenfeld,[1,3] J. Newsom-Davis,[5] J. B. Posner[1,3] and J. Dalmau [1,3]

Departments of [1]Neurology and [2]Pathology, Memorial Sloan-Kettering Cancer Center, and [3] Department of Neurology and Neurosciences, Cornell University Medical College, New York, USA, [4]Service of Neurology, Hospital Clínic i Provincial, University of Barcelona, Spain, [5]Neurosciences Group, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK, [6]Centre de Recherche sur l'Ataxie, Hôpital Neurologique et Neuro-Chirurgical Pierre Wertheimer, Lyon, [7]Service de Neurologie-Div. MAZARIN, Hôpital de la Salpêtriere, Paris and [8]Service de Neurologie, Hôpital de Bellevue, Saint Etienne, France

Correspondence to: Josep Dalmau, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Summary

Several cancers, especially lung, ovarian and breast, can cause paraneoplastic cerebellar degeneration. The presence of different antineuronal antibodies associated with different cancers and paraneoplastic cerebellar degeneration suggests that several immunological mechanisms may result in the same neurological disorder. In patients with small-cell lung cancer, paraneoplastic cerebellar degeneration may occur with or without Hu antineuronal antibodies (HuAb), indicating that patients with the same tumour can develop paraneoplastic cerebellar degeneration by different immunological mechanisms. Furthermore, paraneoplastic cerebellar degeneration sometimes occurs in association with the Lambert–Eaton myasthenic syndrome. In order to try to understand the clinical implication of antineuronal antibodies in patients with small-cell lung cancer, we examined the serum of 57 patients with presenting symptoms of paraneoplastic cerebellar degeneration for the presence of HuAb and P/Q- and N-type voltage-gated calcium channel antibodies. Patients with paraneoplastic cerebellar degeneration who were HuAb positive were compared with HuAb negative patients with respect to neurological symptoms, course of the neurological disorder, response to treatment, tumour prognosis, pathological findings, and cause of death. The tumour outcome and serological findings of these patients were also compared with those of 109 small-cell lung cancer patients without paraneoplastic syndromes of the CNS. Titres of HuAb were classified as 'high' (immunoblot titre >1 : 10 000) or 'low' (<1 : 10 000), the latter similar to the antibody titres detected in some small-cell lung cancer patients without paraneoplastic symptoms. Twenty-five patients with paraneoplastic cerebellar degeneration (44%) had high titres of HuAb, four (7%) had low titres of HuAb, and 28 (49%) were HuAb negative; for clinical comparisons with the patients with high titres of HuAb, the four patients with low antibody titres were included in the HuAb negative cohort. None of the 109 small-cell lung cancer patients without paraneoplastic symptoms had high titres of HuAb. The presence of high titres of HuAb defined a subset of patients who differed from the HuAb negative paraneoplastic cerebellar degeneration cohort, HuAb positive patients were more likely to be female ($P < 0.01$), to have multifocal neurological disease (brainstem encephalopathy and sensory neuropathy being common extracerebellar manifestations) ($P < 0.002$), and be severely disabled ($P < 0.005$). A total of nine patients (16%) from both paraneoplastic cerebellar degeneration groups developed electrophysiologically confirmed Lambert–Eaton myasthenic syndrome. Seven of these nine patients had serum available for P/Q-type voltage-gated calcium channel antibody testing and all seven were positive. In addition, 20% of HuAb

negative paraneoplastic cerebellar degeneration patients without clinically identified Lambert–Eaton myasthenic syndrome had P/Q-type voltage-gated calcium channel antibodies, while only 2% of small-cell lung cancer patients without paraneoplastic symptoms had these antibodies. Treatment of the tumour and/or immunomodulation did not alter the course of paraneoplastic cerebellar degeneration, but improved Lambert–Eaton myasthenic syndrome symptoms. At the time of death, in 60% of HuAb positive and 20% of HuAb negative paraneoplastic cerebellar degeneration patients, the tumour was either not evident or localized to the chest ($P < 0.007$*); neurological disease was the cause of death of 65% HuAb positive paraneoplastic cerebellar degeneration and 10% HuAb negative paraneoplastic cerebellar degeneration patients (*$P < 0.001$*). Irrespective of the serological findings and cause of death, paraneoplastic cerebellar degeneration patients who received standard treatment for the small-cell lung cancer, had shorter survival (1- and 2-year survival after cancer diagnosis of 46% and 28%, respectively) than an age-, tumour-stage- and treatment-matched group of 59 small-cell lung cancer patients without paraneoplastic disease (1- and 2-year survival estimates, 76% and 31%, respectively). The pathological findings of five HuAb positive paraneoplastic cerebellar degeneration patients examined at autopsy included diffuse encephalomyelitis with severe loss of Purkinje cells in four patients, but no apparent Purkinje cell loss in one; three patients also had involvement of posterior nerve roots or dorsal root ganglia. By contrast, autopsy studies of three HuAb negative paraneoplastic cerebellar degeneration patients demonstrated severe loss of Purkinje cells without inflammatory infiltrates of the neuraxis (two patients); mild perivascular inflammatory infiltrates involving dentate, brainstem and spinal cord were found in one patient who died within 1 month of symptom development. We conclude that in patients with small-cell lung cancer and paraneoplastic cerebellar degeneration: (i) the HuAb may or may not be present at high titre (*$>1 : 10\,000$*); (ii) at least 16% of these patients had Lambert–Eaton myasthenic syndrome, irrespective of the HuAb status; (iii) all Lambert–Eaton myasthenic syndrome patients were P/Q-type voltage-gated calcium channel antibody positive; (iv) a further 20% of HuAb negative paraneoplastic cerebellar degeneration patients without identified Lambert–Eaton myasthenic syndrome were also P/Q-type voltage-gated calcium channel antibody positive, suggesting that they had subclinical Lambert–Eaton myasthenic syndrome; (v) HuAb positive paraneoplastic cerebellar degeneration patients were more likely to be female, to have multifocal neurological disease, to be severely disabled, or to die from neurological causes; (vi) independent of serology and cause of death, paraneoplastic cerebellar degeneration patients receiving standard treatment for small-cell lung cancer died earlier than a matched group of non-paraneoplastic cerebellar degeneration small-cell lung cancer patients; (vii) (pathology) inflammatory infiltrates were far more prominent in HuAb positive compared with HuAb negative paraneoplastic cerebellar degeneration patients, in a small series (*$n = 8$*).*

Keywords: paraneoplastic cerebellar degeneration; cancer; Lambert–Eaton myasthenic syndrome

Abbreviations: HuAb = Hu antineuronal antibodies; ω-CmTx = ω-conotoxin MVIIC

Introduction

'Subacute cerebellar degeneration associated with neoplasms', now usually called paraneoplastic cerebellar degeneration, is a clinico-pathological concept established by Brain and Wilkinson (1965), and characterized by the subacute onset of cerebellar dysfunction (gait difficulty and limb ataxia), sometimes associated with dysarthria, dysphagia, nystagmus, mental changes, and muscular and sensory deficits. The pathological hallmark is a diffuse loss of Purkinje cells, usually accompanied by thinning of the molecular and granular layers, and degeneration of the dentate, olivary nuclei and long tracts of the spinal cord (Brain and Wilkinson, 1965). In some patients, inflammatory infiltrates are found in cerebellum and other areas of the neuraxis, but not in the Purkinje cell layer (Brain *et al*., 1951; Vick *et al*., 1969). Cancers of the lung, ovary, breast and lymphoma are the most frequent causal neoplasms. Brain and Wilkinson (1965) included 13 clinically observed cases and six patients with autopsy studies in their original description, and pointed out that subacute cerebellar degeneration associated with neoplasm 'is both clinically and pathologically less well defined than its name may imply'.

In 1982, Henson and Urich classified paraneoplastic cerebellar degeneration according to the presence or absence of inflammatory infiltrates. The discovery that some patients with paraneoplastic cerebellar degeneration harbour, in their serum and CSF, antibodies against neuronal proteins expressed by the tumour (onconeural antigens) (Trotter *et al*., 1976; Greenlee and Brashear, 1983; Graus *et al*., 1985; Jaeckle *et al*., 1985; Luque *et al*., 1991), has lead some investigators (Hammack *et al*., 1990; Dalmau and Graus, 1995; Posner, 1995) to divide paraneoplastic cerebellar degeneration into subsets according to the presence or absence of specific antibodies. While the role of these antibodies in the pathogenesis of paraneoplastic cerebellar degeneration is unknown, specific onconeural antibodies are associated with specific neoplasms, often allowing early detection of the tumour (Hammack *et al*., 1990; Dalmau *et al*., 1992*a*; Peterson *et al*., 1992). In addition, paraneoplastic cerebellar degeneration associated with specific onconeural antibodies differ neuropathologically and clinically. For example, anti-Yo antibodies are usually associated with: (i) ovarian or

breast cancer; (ii) severe neurological disability that is of itself rarely the cause of death; and (iii) a total, or near total loss of Purkinje cells with few or no inflammatory infiltrates in the cerebellum, but marked inflammatory infiltrates in the tumour (Hetzel *et al*., 1990; Peterson *et al*., 1992; Verschuuren *et al*., 1996). By contrast, Hu antineuronal antibodies (HuAb) usually indicate a more widespread disorder called paraneoplastic encephalomyelopathy and sensory neuronopathy, almost always associated with small-cell lung cancer (Anderson *et al*., 1988; Dalmau *et al*., 1992*b*). These patients also differ from anti-Yo patients in that the HuAb positive patients often die from the neurological disorder, and have extensive inflammatory infiltrates in the nervous system and neuronal degeneration not restricted to Purkinje cells of the cerebellum (Graus *et al*., 1987; Anderson *et al*., 1988; Dalmau *et al*., 1992*b*, 1995).

A previous study demonstrated that 13% of patients with small-cell lung cancer and encephalomyelitis present with a subacute cerebellar syndrome that in the initial stages could not be differentiated from paraneoplastic cerebellar degeneration. This study suggested that the presence of HuAb predicted the development of encephalomyelitis (Dalmau *et al*., 1992*b*). Other studies suggested that patients with small-cell lung cancer who develop isolated cerebellar dysfunction are HuAb negative and are more likely to develop Lambert–Eaton myasthenic syndrome (Clouston *et al*., 1992; Motomura *et al*., 1995).

To determine the clinical implication of the presence or absence of antineuronal antibodies in patients presenting with paraneoplastic cerebellar degeneration, we examined the sera of 57 patients with paraneoplastic cerebellar degeneration and small-cell lung cancer for autoantibodies, including HuAb, P/Q- and N-type voltage-gated calcium channel antibodies. Patients with and without HuAb were compared with respect to neurological symptoms, course of the neurological disorder, response to treatment, tumour prognosis, and cause of death.

Patients and methods

Inclusion criteria

Patients included in the study had (i) presenting symptoms of paraneoplastic cerebellar degeneration, (ii) a small-cell lung cancer identified before or after the development of neurological symptoms and (iii) serum available for immunological studies.

Patients were considered to have paraneoplastic cerebellar degeneration if (i) cerebellar dysfunction was not ascribable to structural lesions such as brain or leptomeningeal metastases, cerebellar infarcts, or other identifiable neurodegenerative, toxic, metabolic or iatrogenic diseases, and (ii) the cerebellar syndrome was the initial or main clinical manifestation (if other neurological symptoms were present, these were mild at presentation, or developed later). Clinical disability at presentation was estimated using the modified Rankin Scale (Uchuya *et al*., 1996).

The diagnosis of small-cell lung cancer was confirmed histologically before death in 50 patients. Three patients had tissue diagnosis established at autopsy. Four patients without histological evidence of small-cell lung cancer, were included in the study on the basis of the presence of chest or CT radiological abnormalities suggestive of a neoplasm and the detection of HuAb, which is known to be a serological marker for small-cell lung cancer (Dalmau *et al*., 1990, 1992*a*; Kiers *et al*., 1991).

Using these criteria, 57 patients with small-cell lung cancer and paraneoplastic cerebellar degeneration were identified; 32 were examined by at least one of the authors; information on the other 25 patients whose serum was referred for assay, was obtained from records sent by referring physicians or by telephone and letter interviews with the families or patients. Seven patients with paraneoplastic cerebellar degeneration have been previously reported (Dalmau *et al*., 1991, 1992*b*; González del Val *et al*., 1992; Hersh *et al*., 1994; Heidenreich *et al*., 1995). As controls we included 109 small-cell lung cancer patients without clinical evidence of paraneoplastic cerebellar degeneration or paraneoplastic encephalomyelitis and sensory neuropathy, treated at the Memorial Sloan-Kettering Cancer Center.

Sera and tissues

Serum from paraneoplastic cerebellar degeneration patients was obtained at diagnosis of the neurological disorder, and from control subjects at diagnosis of small-cell lung cancer; all sera were kept frozen at –70°C. Cerebral cortex, cerebellum and non-neural tissue (liver, kidney) were obtained from neurologically normal individuals within 6 h after death, embedded in optimal cutting temperature compound (OCT, Miles, Elkhart, Ind., USA), snap frozen in isopentane chilled by liquid nitrogen, and stored at –70°C. Isolation of cortical neurons and Purkinje cells and purification of recombinant HuD (an antigen recognized by HuAb) were obtained as previously reported (Dalmau and Rosenfeld, 1995; Manley *et al*., 1995).

The sera of all small-cell lung cancer patients (57 with paraneoplastic cerebellar degeneration and 109 without paraneoplastic cerebellar degeneration) and 45 normal individuals (blood bank donors) were examined for antineuronal antibodies at the Memorial Sloan-Kettering Cancer Center (*see* below). In addition, sera were examined for P/Q- and N-type voltage-gated calcium channel antibodies at the Institute of Molecular Medicine, Oxford; they included, 50 sera from small-cell lung cancer patients with paraneoplastic cerebellar degeneration (seven sera were no longer available), and 49 randomly selected sera of the 109 small-cell lung cancer patients without paraneoplastic cerebellar degeneration. Clinical information was concealed from investigators interpreting the results of the studies (J.D., B.L. and J.N.-D.).

Immunohistochemistry

Immunohistochemical studies on sections of human cerebral cortex, cerebellum and non-neural tissues, using serial dilutions (starting at 1 : 500) of sera from patients and controls, were carried out as previously reported (Dalmau *et al*., 1992*a*).

Western blotting

Western blot studies included proteins from isolated cortical neurons (100 μg/lane), Purkinje cells (100 μg/lane), and HuD purified protein (2.3 μg/lane). The indicated amounts of proteins were electrophoretically separated in a 10% sodium dodecyl sulphate–polyacrylamide gel and transferred to nitrocellulose (Towbin *et al*., 1979). After blocking with 5% Carnation milk (Carnation Company, Calif., USA) and 10% normal goat serum (Cappel, West Chester, Pa., USA), strips were sequentially incubated with the patient's serum (serial dilutions, in 10% normal goat serum, starting at 1 : 1000) for 12 h at room temperature, biotinylated goat anti-human IgG (Vector Labs, Burlingame, Calif., USA) diluted 1 : 2000 in 10% normal goat serum, for 1 h at room temperature, and the avidin–biotin–peroxidase complex (Vector Labs) for 30 min at room temperature. The substrate staining was developed with 0.05% diaminobenzidine tetrahydrochloride (Sigma, St Louis, Mo., USA), 0.5% Triton X-100, and 0.01% hydrogen peroxide in PBS (phosphate-buffered saline). Sera from normal individuals and control small-cell lung cancer patients were similarly handled and used at the same dilutions.

Detection and quantification of P/Q- and N-type voltage-gated calcium channel antibodies

To determine P/Q-type voltage-gated calcium channel antibodies, synthetic ω-conotoxin MVIIC (ω-CmTx) was obtained from the Peptide Institute Inc (European Distributor, Scientific Marketing, UK). ^{125}I-labelled ω-CmTx (^{125}I-ω-CmTx) was purchased from Amersham International (Amersham, UK; specific activity 2000 Ci/mmol). Human cerebellum obtained at autopsy of a neurologically normal individual was homogenized in 25 mM Tris–HCl/5 mM HEPES buffer, pH 7.4, containing 0.32 M sucrose, 1 μM pepstatin, 2 μM leupeptin, 0.1 mM phenylmethysulphonyl-fluoride and 20 μg/ml soybean trypsin inhibitor, and centrifuged. The resulting membrane pellets were resuspended in the same buffer with 2% digitonin and agitated for 1 h at 4°C. The supernatant was separated by centrifugation at 13 000 r.p.m. for 10 min. Cerebellum extract (5 μl) containing ~5 fmol of binding sites, was labelled with ^{125}I-ω-CmTx for 2 h (0.1 nM) and incubated overnight with serum (1.25–10 μl diluted 1 : 10) from small-cell lung cancer patients with paraneoplastic cerebellar degeneration or controls. Excess goat anti-human IgG serum was then added for 1 h at 4°C to precipitate serum antibodies. Each sample was centrifuged and the pellets washed twice with 20 mM phosphate buffer pH 7.4 containing 0.1% Triton X-100, before counting. All steps were performed at 4°C. The specific binding was calculated from the total ^{125}I-ω-CmTx precipitated minus the non-specific binding determined by performing the assay in the presence of excess unlabelled ω-CmTx (100 nM). Each sample was examined twice for this assay and the final titre taken as the average of both values.

To determine N-type voltage-gated calcium channel antibodies we used ^{125}I-ω-conotoxin GVIA (^{125}I-ω-CgTx), with an assay identical to the one described above, except that homogenate of human frontal cortex was used as a source of antigen. Each sample was examined once for this assay.

Criteria for the presence of autoantibodies

Sera were considered positive for HuAb when they (i) specifically reacted with neuronal nuclei at dilutions greater than 1 : 500 (reactivity at lower dilutions, sometimes associated with glial staining, was considered nonspecific), and (ii) identified a set of 35 to 40 kDa proteins on immunoblots of cerebral cortex neurons and Purkinje cells or reacted with immunoblots of recombinant HuD protein. Immunoblot reactivity was visually evaluated; a serum was defined as having a low HuAb titre when reactivity could only be detected at dilutions $<$1 : 10 000; a high HuAb titre was defined as positive reactivity at serum dilutions $>$1 : 10 000.

For the P/Q- and N-type voltage-gated calcium channel assays, each serum was defined as positive if the titre was $>$3 SDs above the mean for 20 healthy controls (20 pM for the former and 30 pM for the latter assay).

Statistics

Statistical analyses were performed using Statview 4.5 (Abacus Concepts, Berkeley, Calif., USA). Data pertaining to patient demographics, symptom duration, and outcome were analysed using the Student's *t* test and the Mann–Whitney *U* test. *Post hoc* testing was performed using Fisher's protected least-significant difference. Nominally characterized outcomes were compared using contingency table analysis including the χ^2 test and Fisher's exact test. Kaplan–Meier estimates of overall survival, and survival following the diagnosis of cancer were compared using a stratified Mantel–Haenszel statistic. Statistical significance was defined as $P < 0.05$.

Results

Laboratory findings

Antineuronal antibodies

The serum of 25 paraneoplastic cerebellar degeneration patients had high immunoblot titres of HuAb; four had low titres, and 28 were negative (Fig. 1). Of 109 small-cell lung

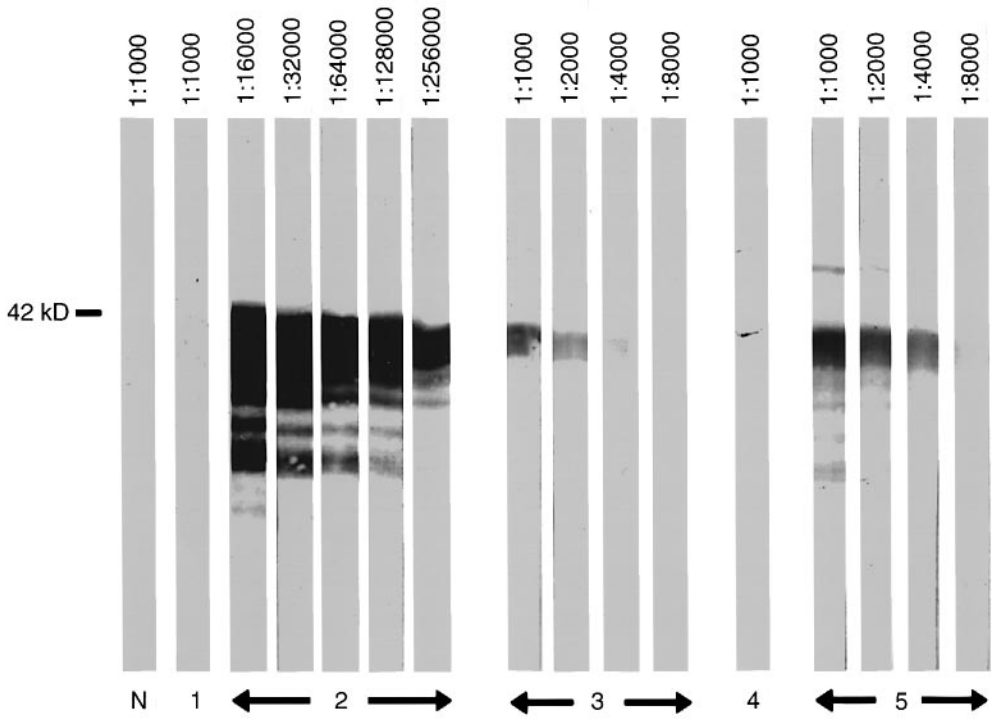

Fig. 1 Western blot of HuD. Immunoblots of HuD reacted with serial dilutions of serum from a patient with paraneoplastic cerebellar degeneration and a high titre of HuAb (lanes 2), serum from a patient with paraneoplastic cerebellar degeneration and low titre of HuAb (lanes 3), and serum from a small-cell lung cancer patient without paraneoplastic symptoms but with low titre of HuAb (lanes 5). Note the difference of reactivity between the patient with high titre of HuAb (lanes 2) and the two patients with low titre of HuAb (lanes 3 and 5). Lane N corresponds to serum from a normal individual; lane 1, serum from a patient with paraneoplastic cerebellar degeneration without HuAb, and lane 4, serum from a small-cell lung cancer patient without HuAb and no paraneoplastic symptoms. Note the absence of HuD reactivity in these three sera (lanes N, 1 and 4).

cancer patients without paraneoplastic cerebellar degeneration or paraneoplastic encephalomyelitis and sensory neuropathy, 19 (17%) had low immunoblot titres of HuAb, and 90 were negative. All 45 sera from normal individuals were negative.

All HuAb positive sera reacted immunohistochemically with cerebral cortical neurons and Purkinje cells, but not with non-neural tissue, as previously reported (Fig. 2A) (Graus *et al*., 1985). Immunoreactivities other than HuAb were identified in the serum of 14 patients with small-cell lung cancer and paraneoplastic cerebellar degeneration, and in the serum of 10 patients with small-cell lung cancer without paraneoplastic symptoms; they included, immunostaining of the cytoplasm of basket cells (five patients, one with high-titre HuAb), cytoplasm of neurons or Purkinje cells (six patients), nuclei of glial cells (eight patients), cytoplasm of glial cells (one patient), and non-neuronal specific nuclear immunostaining (four patients). Due to the variety of reactivities, the small number of patients with a specific pattern of reactivity, and the fact that similar reactivities were detected in patients without paraneoplastic symptoms, the clinical implication of the presence of these antibodies was not investigated.

To determine the clinical significance of classifying paraneoplastic cerebellar degeneration according to the presence or absence of HuAb, we established two groups of patients; those with high titres of HuAb (HuAb positive paraneoplastic cerebellar degeneration), and those without, or with low, titres of HuAb (HuAb negative paraneoplastic cerebellar degeneration). We included four patients with paraneoplastic cerebellar degeneration and low titres of HuAb in the later group because (i) the amount of HuAb was similar, or lower, than in 17% small-cell lung cancer patients without paraneoplastic symptoms, and (ii) previous studies have shown that the HuAb, at low titre, is a marker of the presence of a small-cell lung cancer rather than paraneoplastic symptoms (Dalmau *et al*., 1990; Graus *et al*., 1996).

Voltage-gated calcium channel antibodies

Twelve of 50 paraneoplastic cerebellar degeneration patients tested (24%) had P/Q-type voltage-gated calcium channel antibodies; nine of these patients (18% of the 50) also had N-type voltage-gated calcium channel antibodies. No patient had N-type voltage-gated calcium channel antibodies in isolation. Among the 49 small-cell lung cancer patients without paraneoplastic cerebellar degeneration (control group), one patient (2%) had P/Q-, but no N-type voltage-gated calcium channel antibodies (Fig. 3).

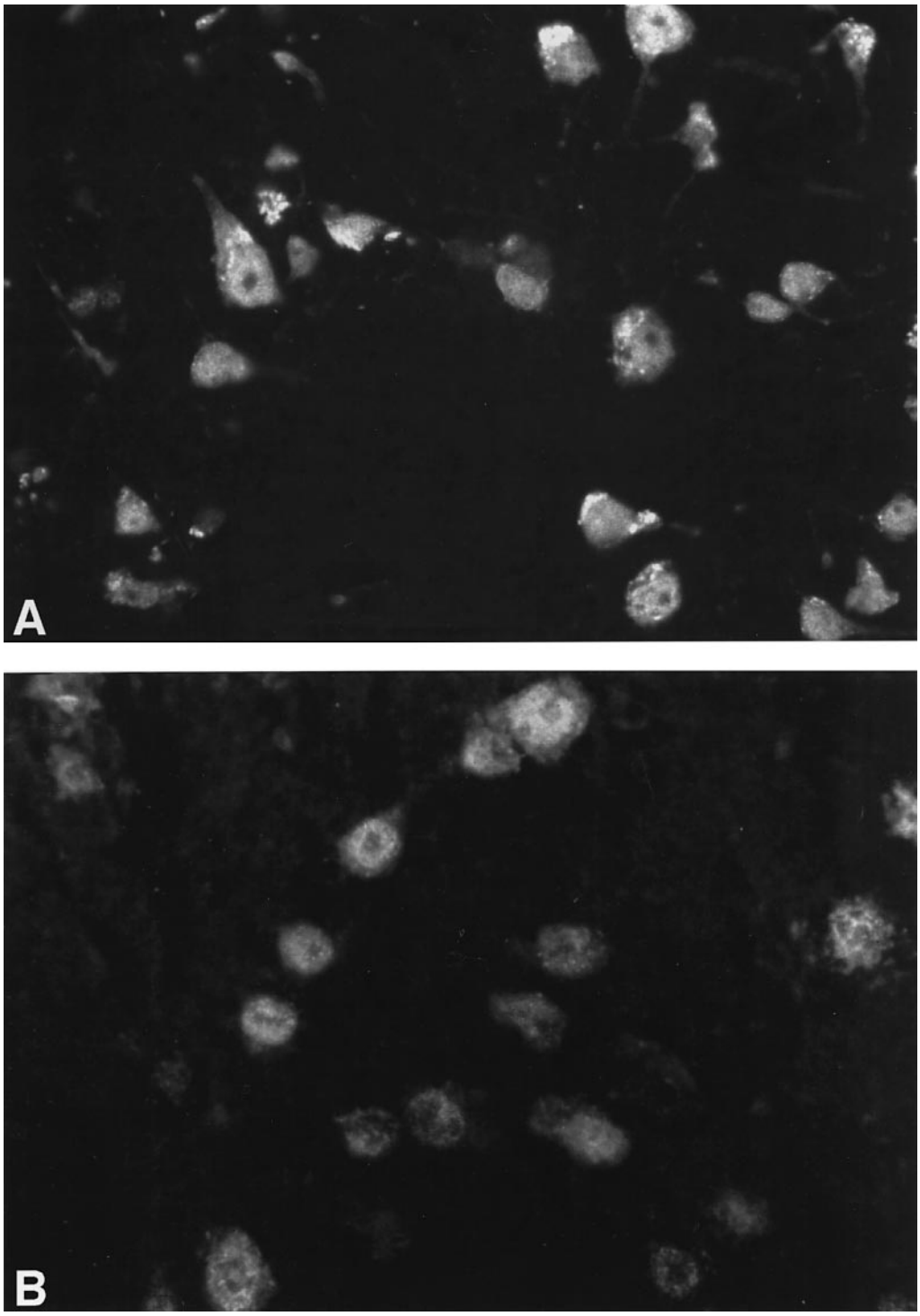

Fig. 2 Immunofluorescence reactivity of HuAb. (**A**) Section of guinea pig cerebral cortex reacted with serum from a small-cell lung cancer patient with paraneoplastic cerebellar degeneration, sensory neuropathy, and HuAb. (**B**) Photomicrograph of Wilkinson and Zeromski, published in *Brain* (Wilkinson and Zeromski, 1965) demonstrating reactivity of the serum of a patient with lung cancer and paraneoplastic sensory neuropathy with a section of guinea pig cerebral cortex. Note that the reactivity is similar to that of the HuAb (**A**) characterized by predominant immunolabelling of the neuronal nuclei (sparing the nucleoli) and weaker reactivity with the cytoplasm of neurons. (**B** has been reproduced with permission.)

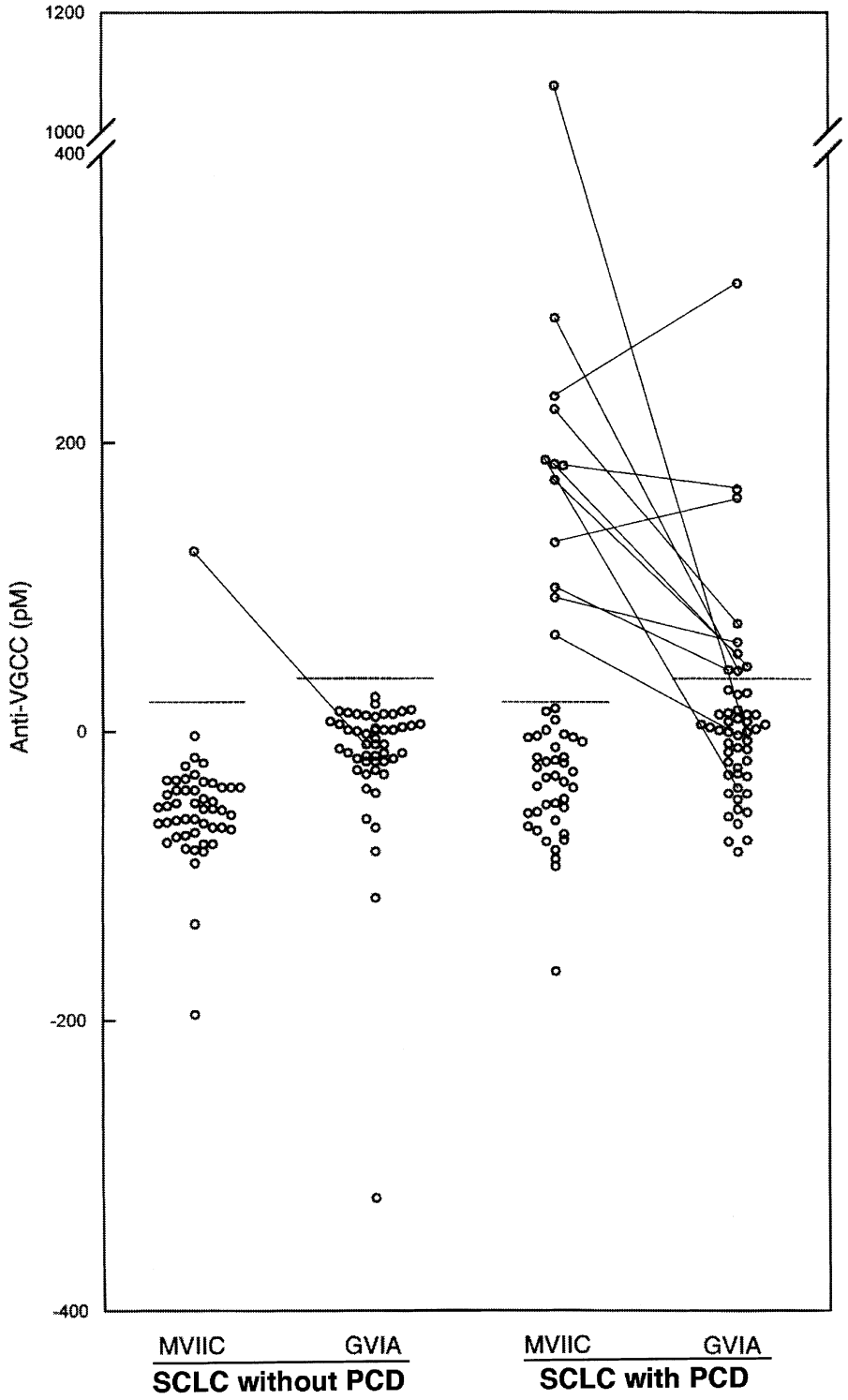

Fig. 3 Quantification of P/Q- and N-type voltage-gated calcium channel (VGCC) antibodies in 50 small-cell lung cancer (SCLC) patients with paraneoplastic cerebellar degeneration (PCD) and 49 small-cell lung cancer patients without paraneoplastic cerebellar degeneration. Twelve (24%) paraneoplastic cerebellar degeneration patients had P/Q type voltage-gated calcium channel antibodies; nine (18%) of these patients had also N-type voltage-gated calcium channel antibodies. Only one small-cell lung cancer patient (2%) without paraneoplastic cerebellar degeneration had P/Q-type voltage-gated calcium channel antibodies. Sera were defined positive for P/Q type (MVIIC) voltage-gated calcium channel antibodies if the titre was >3 SDs (20 pM) above the mean for 20 healthy controls. Sera were defined positive for N-type (GVIA) voltage-gated calcium channel antibodies if the titre was >3 SD (30 pM) above the mean for the same healthy controls.

Table 1 *Clinical features of paraneoplastic cerebellar degeneration (PCD) in patients with small-cell lung cancer (SCLC)*

	HuAb$^+$PCD (25)	HuAb$^-$PCD (32)	*P*-values
Sex (men : women)	12 : 13	26 : 6	$P < 0.01$
Age: median (range)	66 (47–80)	62 (49–85)	
Onset of neurological symptoms (before/after SCLC)	22/3	27/5	
Stage of SCLC			
Limited : extensive	23 : 1	25 : 6	
Unknown	1	1	
Development of PCD			
Acute (1–7 days)	1	6	
Subacute (7 days to 1 month)	24	25	
Chronic (>1 month)	0	1	
Neuroradiology and/or CSF at time of PCD diagnosis	25	32	
CT alone	5	4	
MRI alone	9 (5 PWM, Abn^1)	14 (2 PWM)	
CT and MRI	11 (1 PWM, Abn^2)	14 (1 PWM, Abn^3)	
CSF	23 (20 Infl.; 3 normal)	22 (13 Infl.; 9 normal)	
Presenting clinical features			
Cerebellar:	25	32	
axial ataxia	25	31	
appendicular ataxia	24	27	
nystagmus	16	18	
dysarthria	13	19	
diplopia without LEMS or other brainstem signs	4	5	
Extracerebellar:	20 (80%)	12 (37.5%)	$P < 0.002$
Higher cortical	6 (2 seizures)	3 (1 seizure)	
Brainstem*	7†	2‡	$P < 0.03$
Motor weakness (other than LEMS)	4	1	
Corticospinal (Babinski)	1	2	
Sensory neuropathy	10	2	$P < 0.002$
Autonomic (other than LEMS)	5	2	
LEMS	4	5 (2 with diplopia)	
Severity of neurological deficit			
At presentation (Rankin scale) median (range)	4 (3–5)	3 (2–5)	
Later, assistance (for basic activities)	18/25	11/32	$P < 0.005$

LEMS = Lambert–Eaton myasthenic syndrome. HuAb$^+$PCD = PCD patients with high titres of HuAb; HuAb$^-$PCD = PCD patients without HuAb or with low titres of HuAb. PWM = periventricular white matter changes. Infl. = inflammatory changes (increased proteins and/or pleocytosis). Abn^1 = abnormal T_2-signal in the pons and right internal capsule in a patient with PCD, opsoclonus and encephalopathy; Abn^2 = abnormal T_2-signal in the right insula of a patient with limbic encephalopathy; Abn^3 = transient T_2-abnormalities in the right temporal and semioval areas of a patient with limbic encephalopathy. *Excludes patients with LEMS or isolated diplopia. †Seven HuAb$^+$PCD patients: diplopia (four patients), anosmia (one), facial weakness with signs of denervation (two), oculomotor palsy (one), dysphagia (four), opsoclonus (two), palatal myoclonus (one), spontaneous slow vertical eye movements (one), sensory loss in trigeminal nerve distribution (one). ‡Two HuAb$^-$PCD patients: diplopia (two patients), head bobbing (one), horizontal conjugate gaze palsy (one).

Clinical features

Age and sex

There was no age difference between the HuAb positive and HuAb negative paraneoplastic cerebellar degeneration groups (Table 1). The HuAb positive group contained more women, 13 out of 25 (52%), and the HuAb negative more men, 26 out of 32 (81%) ($P < 0.01$, $\chi^2 = 6.983$).

Thirty-one paraneoplastic cerebellar degeneration patients (17 men, 14 women) were from USA and 26 (21 men, five women) from Europe (Spain 15, France 10, and Germany one). The low prevalence of women with small-cell lung cancer in the European patients reflects the low exposure to tobacco smoking among women of that age (i.e. all 15 Spanish patients were men) (Ruigomez *et al*., 1995). When the patients from the USA were considered, we found that nine out of 14 HuAb positive paraneoplastic cerebellar degeneration (64%) were women and 12 out of 17 HuAb negative paraneoplastic cerebellar degeneration (71%) were men ($P = 0.05$, $\chi^2 = 3.770$). The 109 small-cell lung cancer controls were 57 men and 52 woman (i.e. 52% male).

Features relating to the paraneoplastic cerebellar degeneration

Because neurological symptoms preceded the cancer diagnosis in 49 patients (22 HuAb positive and 27 HuAb negative paraneoplastic cerebellar degeneration), most patients underwent extensive blood and CSF analysis, and radiological evaluation of the nervous system, chest and abdomen either as part of the neurological diagnosis or as

tumour staging (Table 1). All patients had neuroradiological studies (57 patients) and/or CSF analysis (45) without evidence of intracranial or leptomeningeal metastases. Cerebellar atrophy was identified at onset in only one patient who had diffuse cerebral atrophy. Signs of cerebellar atrophy were identified 6 months after symptom development in nine patients; the MRI of two patients remained normal 2 years after developing paraneoplastic cerebellar degeneration.

Neurological complaints antedated the cancer diagnosis by a median of 3 months (range 1–10 months for HuAb positive paraneoplastic cerebellar degeneration; 1–26 months for HuAb negative paraneoplastic cerebellar degeneration). In eight patients (three with HuAb positive and five with HuAb negative paraneoplastic cerebellar degeneration) neurological symptoms developed after tumour diagnosis (range 1–12 months, median 5 months). At the time of tumour diagnosis, most patients had limited stage disease (cancer confined to the chest) (Table 1).

Ataxia was detected at presentation in all paraneoplastic cerebellar degeneration patients. Nystagmus, usually asymptomatic, was present in 64% HuAb positive and 56% HuAb negative paraneoplastic cerebellar degeneration patients. Dysarthria, sufficient to interfere with communication, was present in 52% HuAb positive and 59% HuAb negative patients. Diplopia was an early and frequent symptom in both groups of patients.

Overall, 80% HuAb positive and 37.5% HuAb negative paraneoplastic cerebellar degeneration patients developed extracerebellar symptoms during the course of the disease ($P < 0.002$, $\chi^2 = 10.296$). Extracerebellar symptoms were often detectable within the first month of the disease (Table 1), but in some patients developed as the disease evolved. Symptoms and signs of brainstem or cranial nerve dysfunction predominated in HuAb positive patients ($P < 0.03$, $\chi^2 = 4.993$). In addition, one patient with HuAb had bilateral optic neuritis of uncertain origin.

Ten (40%) HuAb positive paraneoplastic cerebellar degeneration patients developed a pure sensory neuropathy. Sensory deficits were present at the beginning of paraneoplastic cerebellar degeneration in nine patients and developed later in one; symptoms evolved asymmetrically in five and were associated with pain in 7. Eventually, the lower extremities were involved in all 10 patients and the upper extremities in seven. One patient had painful dysaesthesias in the face; none developed sensory deficits in the abdomen or trunk. Electrophysiological studies obtained in seven patients showed absent sensory potentials in six (one also had denervation) and normal findings in one. Motor nerve conduction studies were normal or borderline in all patients. The sensory neuropathy became severe in four patients and remained mild or moderate in the other six. By contrast, only two HuAb negative paraneoplastic cerebellar degeneration patients (6%) developed mild distal symmetric sensory neuropathy in the lower extremities (decreased vibratory sensation and absent ankle jerks). Comparing these patients with the HuAb positive patients, the incidence and severity of sensory neuropathy was significantly associated with the presence of HuAb ($P < 0.002$, $\chi^2 = 9.619$).

Typically, patients were disabled and had to make substantial lifestyle modifications. At initial neurological evaluation, the HuAb positive paraneoplastic cerebellar degeneration cohort were more severely disabled than the HuAb negative with median Rankin disability scores of 4 and 3, respectively, but this difference was not significant, $P = 0.10$. However, 18 of 25 HuAb positive (72%) and 11 of 32 HuAb negative paraneoplastic cerebellar degeneration patients (34%) eventually required assistance in performing activities of daily living ($P < 0.005$, $\chi^2 = 7.950$).

Incidence and features of Lambert–Eaton myasthenic syndrome in patients with paraneoplastic cerebellar degeneration

Lambert–Eaton myasthenic syndrome with proximal motor weakness, decreased or absent reflexes, dry mouth, or diplopia (two cases) was clinically identified in eight patients (four HuAb positive and four HuAb negative paraneoplastic cerebellar degeneration). Seven of them had Lambert–Eaton myasthenic syndrome confirmed electrophysiologically (>100% increase of compound muscle action potential after maximum voluntary contraction or high-frequency repetitive nerve stimulation), and in one repetitive nerve stimulation was not obtained. One additional HuAb positive patient had electrophysiological signs of Lambert–Eaton myasthenic syndrome, but suffered from a devastating cerebellar syndrome which masked Lambert–Eaton myasthenic syndrome symptoms (Table 2). Among these nine patients with definite or probable Lambert–Eaton myasthenic syndrome, seven had serum available for assay for voltage-gated calcium channel antibodies; all seven were positive for P/Q-type voltage-gated calcium channel antibodies, and four of them also had N-type voltage-gated calcium channel antibodies. In addition, P/Q-type voltage-gated calcium channel antibodies were identified in five HuAb negative paraneoplastic cerebellar degeneration patients without clinical or electrophysiological (four patients) signs of Lambert–Eaton myasthenic syndrome; all five patients also had N-type voltage-gated calcium channel antibodies.

Overall, eight out of 57 (14%) small-cell lung cancer patients with paraneoplastic cerebellar degeneration had symptoms that led to Lambert–Eaton myasthenic syndrome being identified, compared with none of 49 small-cell lung cancer patients without paraneoplastic cerebellar degeneration ($P < 0.01$, $\chi^2 = 7.439$). Regardless of the presence of symptoms or electrophysiological findings of Lambert–Eaton myasthenic syndrome, 12 of 50 (24%) paraneoplastic cerebellar degeneration patients harboured P/Q-type voltage-gated calcium channel antibodies compared with one out of 49 (2%) small-cell lung cancer patients without paraneoplastic cerebellar degeneration (Fig. 3). Antibodies to voltage-gated calcium channel appeared to be particularly high in the HuAb

Table 2 *Lambert–Eaton myasthenic syndrome and antibodies to voltage-gated calcium channels in patients with small-cell lung cancer and paraneoplastic cerebellar degeneration*

	SCLC with PCD (57)		SCLC without PCD (49)
	$HuAb^+PCD(25)$	$HuAb^-PCD(32)$	
LEMS*	4/25	5/32	0/49
VGCC antibodies			
P/Q-type (MVIIC)	2 (LEMS)/22	10 (5 LEMS)/28	1/49
N-type (GVIA)	1 (LEMS)/22	8 (3 LEMS)/28	0/49
not tested	3 (2 LEMS by EMG)/25	4/32	

LEMS = Lambert–Eaton myasthenic syndrome; PCD = paraneoplastic cerebellar degeneration; SCLC = small-cell lung cancer; VGCC = voltage-gated calcium channel. $P < 0.01$ for frequency of clinically identified LEMS, comparing SCLC patients with PCD (eight out of 57) with SCLC patients without PCD (none of 49 patients) ($\chi^2 = 7.439$). $P < 0.001$ for the presence of P/Q-type VGCC antibodies, comparing $HuAb^-PCD$ patients (10 out of 28) with SCLC patients without PCD (one out of 49 patients) ($\chi^2 = 16.5$). $P < 0.0001$ for the presence of N-type VGCC antibodies, comparing $HuAb^-PCD$ patients (eight out of 28) with SCLC patients without PCD (none of 49 patients). ($\chi^2 = 20.1$). $HuAb^+PCD$ = PCD patients with high titres of HuAb; $HuAb^-PCD$ = PCD patients without HuAb or with low titres of HuAb. *Eight out of nine patients had definite LEMS; seven (four $HuAb^+PCD$ and three $HuAb^-PCD$) had clinical and electrophysiological signs of LEMS, and one $HuAb^-PCD$ had electrophysiological signs of LEMS but symptoms were missed due to severe PCD. Another $HuAb^-PCD$ had probable LEMS based on proximal muscle weakness and absent reflexes, decreased motor unit potentials (repetitive stimulation not obtained), positive P/Q-type VGCC antibodies, and improvement of motor weakness after plasma exchange.

negative paraneoplastic cerebellar degeneration group, in which 10 out of 28 (36%) had P/Q-type voltage-gated calcium channel antibodies ($P < 0.001$, $\chi^2 = 16.5$) and eight of them (29%) also had N-type voltage-gated calcium channel antibodies ($P < 0.0001$; $\chi^2 = 20.1$) (Table 2).

Two patients with Lambert–Eaton myasthenic syndrome responded to therapy; both received plasma exchange, and one 3,4-diaminopyridine. No specific treatment for the Lambert–Eaton myasthenic syndrome was given to two patients; one had severe paraneoplastic cerebellar degeneration and Lambert–Eaton myasthenic syndrome diagnosed electrophysiologically, and the other presented with mild symptoms of Lambert–Eaton myasthenic syndrome 3 months before developing severe paraneoplastic cerebellar degeneration and prior to the diagnosis of small-cell lung cancer. Treatment, if any, and responses are unknown in the other four patients with symptoms of Lambert–Eaton myasthenic syndrome.

Response of paraneoplastic cerebellar degeneration and small-cell lung cancer to cancer therapy or immunotherapy

The responses of paraneoplastic cerebellar degeneration and small-cell lung cancer to treatment are shown in Tables 3 and 4, respectively. Overall, four patients (one with HuAb positive and three with HuAb negative paraneoplastic cerebellar degeneration) had partial neurological improvement; all received treatment for the tumour and three had plasma exchange. Two of these patients (one HuAb positive and one HuAb negative paraneoplastic cerebellar degeneration) had Lambert–Eaton myasthenic syndrome that responded to therapy (*see* above); thus apparent improvement could have been due to amelioration of Lambert–Eaton myasthenic syndrome. No neurological response was observed in nine other patients (five HuAb positive and four HuAb negative paraneoplastic cerebellar degeneration) who received similar treatment for the tumour and plasma exchange.

Survival and cause of death

No significant differences were observed between survival (Table 4) or Kaplan–Meier survival estimates of HuAb positive and negative paraneoplastic cerebellar degeneration patients (data not shown). In total, 31 paraneoplastic cerebellar degeneration patients (14 HuAb positive and 17 HuAb negative) received treatment for limited-stage small-cell lung cancer; 1- and 2-year survival estimates following the cancer diagnosis were 46% (confidence interval 28%–64%) and 28% (confidence interval 10%–46%), respectively. Survival estimates at 1- and 2-years for an age-, sex- and treatment-matched cohort of 59 neurologically normal patients with limited-stage small-cell lung cancer were 76% (confidence interval 65%–87%) and 31% (confidence interval 19%–43%), respectively (Fig. 4). This finding indicates that 1 year survival for small-cell lung cancer patients with paraneoplastic cerebellar degeneration (regardless of the HuAb status) is less likely than 1 year survival for small-cell lung cancer patients without paraneoplastic cerebellar degeneration.

HuAb positive paraneoplastic cerebellar degeneration patients were significantly more likely than HuAb negative to die of neurological disease ($P < 0.001$, $\chi^2 = 12.907$) (Table 4). Thirteen of 20 HuAb positive died of neurological causes, including respiratory muscle failure due to lower motor neuron dysfunction (two patients needed ventilatory support), autonomic failure (two) and progressive diffuse

Table 3 *Response of paraneoplastic cerebellar degeneration to treatment*

Response	$HuAb^+$PCD patients (25)		$HuAb^-$PCD patients (32)*	
	Not treated (6)	Treated (19)	Not treated (3)	Treated (27)
Stable	3	12	1	13
on tumour treatment		7		9
on PCD treatment		1		–
on both treatments		4		4
Partial improvement†	0	1	0	3
on tumour treatment		–		1
on PCD treatment		–		–
on both treatments		1		2
Deterioration	2	3	1	5
on tumour treatment		1		5
on PCD treatment		1		–
on both treatments		1		–
Not evaluable‡	1	3	1	6
on tumour treatment		2		6
on PCD treatment		–		–
on both treatments		1		–

Treatment of the tumour only = chemotherapy ± chest radiotherapy; treatment of PCD only = corticosteroids, plasma exchange, intravenous IgG. $HuAb^+$PCD = PCD patients with high titres of HuAb; $HuAb^-$PCD = PCD patients without HuAb or with low titres of HuAb. *Unknown in two patients. †Two of the four patients with partial neurological improvement had LEMS. ‡Neurological response to treatment could not be evaluated in three $HuAb^+$PCD patients (one died from complications of chemotherapy and two were lost to follow-up) and six $HuAb^-$PCD patients (one died from complications of chemotherapy, one died from tumour progression before neurological response could be evaluated, one was in complete tumour remission when PCD developed and received no further therapy, and three were lost to follow-up).

Table 4 *Response of small-cell lung cancer (SCLC) to treatment: survival and cause of death*

	$HuAb^+$PCD (25)	$HuAb^-$PCD (32)	*P*-value
Treatment for SCLC			
Patients treated	17	27	
Chemotherapy only	8	10	
Chemo/radiation therapy	9	17	
Response of SCLC to treatment			
Complete	4 (17)	13 (27)	
Other (P/S/Pr)*	8 (6/0/2)	9 (4/1/4)	
Not evaluable‡	1	1	
Unknown	4	4	
Median survival (range)†	13 months (1–84)	15 months (1–88)	
Cause of death			
Neurological	13 (20)	2 (20)	$P < 0.001$
Tumour-related	5	16	
Other‡	1	1	
Unknown	1	1	
Stage of tumour at death			
NED/limited (intrathoracic)	2/10 (20)	1/3 (20)	$P < 0.007$
Extensive (extrathoracic)	7§	16	
Unknown	1	0	

NED = No evidence of neoplastic disease; $HuAb^+$PCD = PCD patients with high titres of HuAb; $HuAb^-$PCD = PCD patients without HuAb or with low titres of HuAb. *P/S/Pr = partial/stable/progressive. †Survival from onset of neurological symptoms (or tumour diagnosis when neurological symptoms developed later) until death. ‡These two patients died from complications of chemotherapy. §In two patients the only evidence of extensive disease was microscopic infiltration of mesenteric lymph nodes.

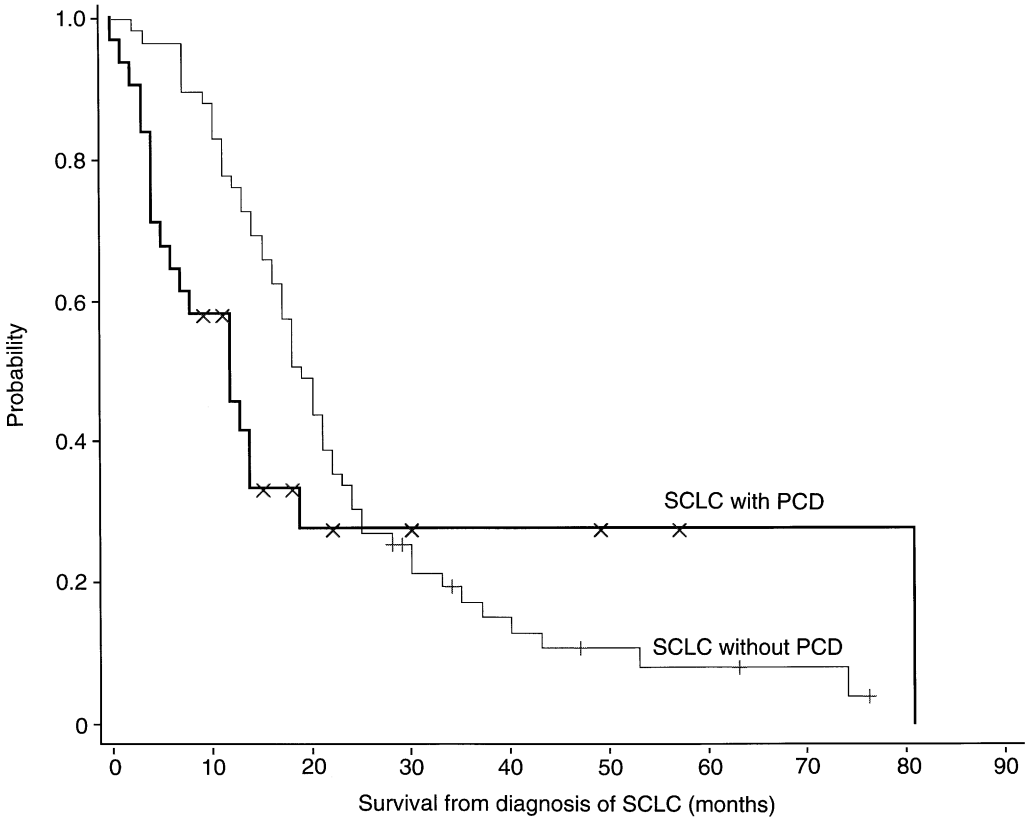

Fig. 4 Kaplan–Meier survival curves of 31 small-cell lung cancer patients (SCLC) with paraneoplastic cerebellar degeneration (PCD), and an age-, sex-, tumour stage- and treatment-matched cohort of 59 small-cell lung cancer patients without paraneoplastic cerebellar degeneration. The thick line represents small-cell lung cancer patients with paraneoplastic cerebellar degeneration and the thin line small-cell lung cancer patients without paraneoplastic cerebellar degeneration. X = censor times for small-cell lung cancer patients with paraneoplastic cerebellar degeneration; + = censor times for small-cell lung cancer patients without paraneoplastic cerebellar degeneration. Note that 1-year survival in small-cell lung cancer patients with paraneoplastic cerebellar degeneration (combined group of 14 HuAb positive and 17 HuAb negative) is less likely than 1-year survival in small-cell lung cancer patients without paraneoplastic cerebellar degeneration.

encephalopathy with predominant brainstem dysfunction (nine). Only two of 20 HuAb negative paraneoplastic cerebellar degeneration patients died as a result of progressive neurological disease (*see* pathology findings in Table 5). By contrast, five HuAb positive and 16 HuAb negative paraneoplastic cerebellar degeneration patients died from tumour progression. Patients with HuAb were also less likely than HuAb negative patients to have extensive small-cell lung cancer at the time of death ($P < 0.007$, $\chi^2 = 7.501$) (Table 4). At death, 12 HuAb positive paraneoplastic cerebellar degeneration patients had either small-cell lung cancer limited to the thoracic cavity (10) or had no evident tumour (two); seven had extensive disease but in two the extent of metastatic dissemination was microscopic, being confined to mesenteric lymph nodes examined at autopsy. The extent of tumour infiltration was unknown at the time of death in one HuAb positive patient. In the HuAb negative paraneoplastic cerebellar degeneration subset, one patient had no evidence of tumour at death, three had limited small-cell lung cancer, and 16 had widely disseminated disease. The extent of small-cell lung cancer dissemination at death in HuAb negative paraneoplastic cerebellar degeneration patients was similar to that in the control patients with initially limited small-cell lung cancer. Of these 59 patients, 53 are deceased; 41 had disseminated disease at death, 10 had small-cell lung cancer confined to the thorax, and two had no evidence of tumour.

Five HuAb positive and seven HuAb negative paraneoplastic cerebellar degeneration patients were alive at last follow-up. One HuAb positive patient has no evidence of small-cell lung cancer (49 months after diagnosis), two have limited and stable disease (12 and 16 months), one has stable liver metastases (12 months), and details are unknown for one patient. Six HuAb negative paraneoplastic cerebellar degeneration patients are currently without evidence of small-cell lung cancer (median 13 months, range 9–30 months), and one is alive with limited and stable disease (6 months).

Pathology

All paraneoplastic cerebellar degeneration patients with a high titre of HuAb had inflammatory infiltrates involving

Table 5 *Neuropathological findings in eight patients with small-cell lung cancer (SCLC) and paraneoplastic cerebellar degeneration (PCD)*

Autopsy number/ gender age (years)	Time between neurological symptoms and death	Main symptoms (CSF, cells, proteins)*	Tumour stage at autopsy (cause of death)	Neuropathology	Antibody group
1/M 70	12 months	PCD Brainstem dysfunction (abnormal, <5, 62)	Limited: mediastinal lymph nodes (neurological)	Inflammatory infiltrates in cerebellar cortex, surrounding Purkinje cells, and dentate nucleus; severe patchy loss of Purkinje cells. Scattered lymphocytic perivascular and interstitial inflammatory infiltrates in meninges, brainstem, spinal cord and dorsal root ganglia. Secondary degeneration of dorsal columns of spinal cord	HuAb+PCD
2/F 60	5 months	PCD Motor neuron syndrome (abnormal, 15, 1200)	Limited: mediastinal lymph nodes (neurological)	Moderate patchy Purkinje cell loss, degeneration of olivary nucleus with gliosis; perivascular lymphocytic infiltrates in amygdala, brainstem (medulla > pons) and spinal cord. Intense gliosis and moderate loss of neurons in the same areas. Loss of neurons and inflammatory infiltrates in anterior horn of the spinal cord	HuAb+PCD
3/F 74	5 months	PCD Opsoclonus, myoclonus Encephalopathy (abnormal, 8, 71)	SCLC in lung and mediastinal lymph nodes. Metastases to liver and pericardium (neurological)	No Purkinje cell loss; normal appearance of Purkinje and granular cells in hemispheric cortex, vermis and flocculus. Normal dentate. Normal cerebellar white matter, except for scanty lymphocytic cells around a few blood vessels. Perivascular lymphocytic infiltrates involving the hypoglossal nerve emerging from medulla, putamen, and meninges overlying orbito-frontal cortex. Spinal cord and dorsal root ganglia not examined	HuAb+PCD
4/F 61	10 months	PCD Sensory symptoms (polyradiculo -neuropathy) (abnormal, 7, 46)	SCLC in lung. Metastases to bone, liver, adrenal gland. (respiratory problems due to local tumour progression)	Marked loss of Purkinje cells; neuronal loss in dentate and olivary nuclei; gliosis of cerebellar white matter and molecular layer. Marked degeneration of dorsal roots and posterior columns of the spinal cord. Partial loss of myelinated fibers of VII and VIII cranial nerves. Marked axonal and demyelinating changes in brachial plexus. Small subdural metastasis in left temporal region, without leptomeningeal or intracerebral metastases	HuAb+PCD
5/F 50	23 months	PCD Limbic encephalopathy (abnormal, <5, <45) (↑ synthesis IgG)	Solitary retroperitoneal adenopathy with SCLC (Neurological)	Marked loss of Purkinje cells. Severe perivascular inflammatory infiltrates in cerebellum, cerebrum (frontal, parietal, temporal lobes, basal ganglia), brainstem (pons), spinal cord, dorsal root ganglia and nerve roots	HuAb+PCD
6/M 65	1 month	PCD Peripheral neuropathy (abnormal, 200, 200)	SCLC. No metastasis (neurological)	Extensive Purkinje cell loss mainly affecting vermis. Scant perivascular lymphocyte cuffing involving dentate, brainstem and spinal cord. Extensive inflammatory infiltrates in the leptomeninges covering brainstem, cerebellum and spinal cord. No apparent neuronal loss in brainstem, spinal cord and dorsal root ganglia	HuAb–PCD Anti-CV2+[†]
7/M 56	5 months	PCD (normal)	SCLC. No metastasis. (Progressive local disease, pneumonia)	Purkinje cell loss, Bergmann gliosis. Mild neuronal loss in molecular layer of cerebellum; no inflammation in cerebellum, cerebrum, brainstem and spinal cord	HuAb–PCD
8/F 65	9 months	PCD Bilateral Babinski. (abnormal, 1100, 1600)	SCLC. No metastasis (neurological)	Extensive Purkinje cell loss. Spinal cord changes: severe degeneration of corticospinal tracts, moderate degeneration of the medial aspect of the anterior columns and ventrolateral aspect of the posterior columns (with foamy macrophage infiltrate). No inflammatory infiltrates at any level of the neuraxis. No neuronal loss in cerebrum, brainstem and spinal cord	HuAb–PCD

*CSF, cells: number/mm^3; proteins mg/dl. [†]Antibody reported associated with paraneoplastic encephalitis (Antoine *et al.*, 1993; Honnorat *et al.*, 1996). HuAb$^+$PCD = PCD patients with high titres of HuAb; HuAb$^-$PCD = PCD patients without HuAb, or with low titres of HuAb.

multiple areas of the nervous system (Table 5); perivascular lymphocytic cuffing was always present in those areas, in association with variable interstitial inflammatory infiltrates and gliosis (Fig. 5). Four of the five HuAb positive patients had moderate to severe loss of Purkinje cells (Fig. 5A and B) associated with inflammatory infiltrates in the deep cerebellar nuclei, particularly dentate (Fig. 5C); infiltrates of T cells adjacent to the Purkinje cell layer were identified in one of these patients (Fig. 5A). In another HuAb positive patient (Table 5, autopsy 3), perivascular cuffing was identified in only a few vessels of the cerebellar white matter; there was no apparent Purkinje cell loss, and the cerebellar cortex and nuclei appeared normal.

In two HuAb negative paraneoplastic cerebellar degeneration patients, the pathological findings were largely restricted to the cerebellum where Purkinje cell loss was prominent in both cases (Fig. 5D), and associated with gliosis in one; no inflammatory infiltrates were identified in the cerebellum, brainstem or brain. The spinal cord, examined in one of these two patients, showed degeneration of the spinal tracts

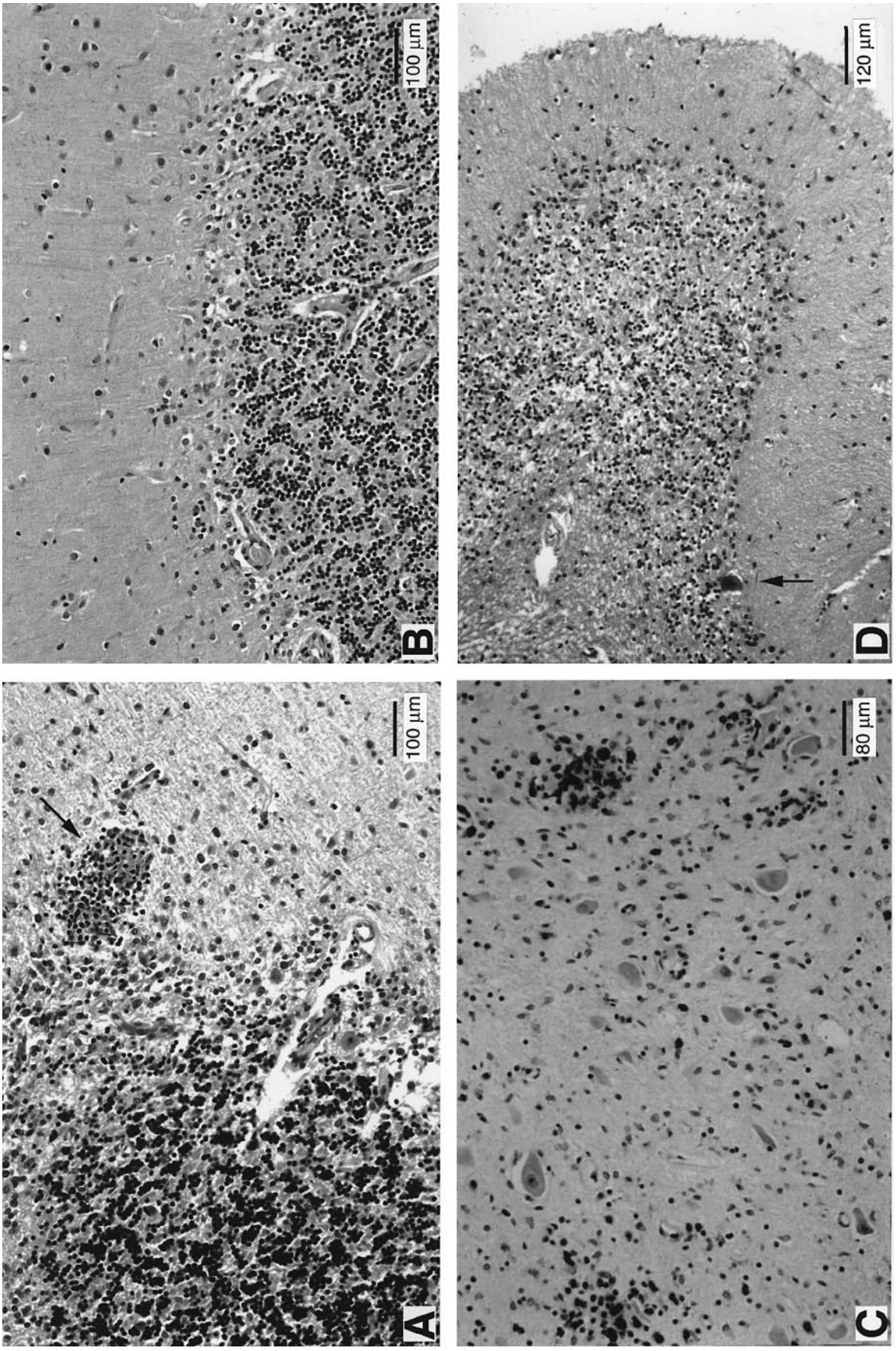

Fig. 5 Neuropathological findings in small-cell lung cancer patients with paraneoplastic cerebellar degeneration. **A–C** are from the cerebellum of a patient with HuAb positive paraneoplastic cerebellar degeneration (autopsy 1). **A** shows a representative infiltrate of mononuclear inflammatory cells (arrow) adjacent to the Purkinje cell layer; **B** shows an area of total loss of Purkinje cells and Bergmann gliosis, and **C** demonstrates infiltrates of T cells in the deep cerebellar nuclei (dentate). **D** is from the cerebellar cortex of a paraneoplastic cerebellar degeneration patient without HuAb (autopsy 8). Note that there is severe depletion of Purkinje cells, without inflammatory infiltrates; a remaining Purkinje cell is marked with an arrow. **A**, **B** and **D** are stained with haematoxylin and eosin. In **C**, the tissue section was incubated with the T-lymphocyte marker UCHL-1, and lightly counterstained with haematoxylin.

(predominantly corticospinal) without inflammatory infiltrates or loss of neurons; the patient did not have any corresponding clinical signs.

A third HuAb negative paraneoplastic cerebellar degeneration patient had extensive Purkinje cell loss associated with perivascular inflammatory infiltrates in several areas of the neuraxis. The serum of this patient contained antibodies, called CV2, which specifically react with the nervous system and have been reported to be associated with paraneoplastic encephalitis (data not shown) (Antoine *et al*., 1993; Honnorat *et al*., 1996). None of the other seven patients with post-mortem studies harboured this antibody in their serum.

Discussion

In patients with small-cell lung cancer, paraneoplastic cerebellar degeneration occurs with or without HuAb. The presence or absence of these antibodies has clinical and prognostic implications and characteristic pathological correlations. However, regardless of the HuAb status, at least 16% of patients develop Lambert–Eaton myasthenic syndrome, and 36% of those without HuAb harbour P/Q- or N-type voltage-gated calcium channel antibodies.

Wilkinson and Zeromski (1965) first reported antineuronal antibodies in patients with paraneoplastic neurological syndromes. The serum of four patients with small-cell lung cancer and sensory neuropathy contained antibodies that appeared to react with neuronal cytoplasmic antigens. They suggested that 'it would be of interest to investigate sera from patients with encephalomyelitic form of carcinomatous neuropathy for the presence of circulating anti-brain antibodies, particularly as lymphocytic infiltration is a prominent feature in these patients' (Wilkinson and Zeromski, 1965). They were correct (Graus *et al*., 1987; Anderson *et al*., 1988; Dalmau *et al*., 1992*b*). Careful inspection of the photomicrograph of the antibody reactivity identified by Wilkinson and Zeromski (1965) suggests that it was HuAb (Fig. 2). HuAb reacts with 35–40 kDa antigens expressed in neurons of the central and peripheral nervous system and in small-cell lung cancer (Graus *et al*., 1986; Dalmau *et al*., 1990, 1992*a*). A high titre of HuAb is usually associated with small-cell lung cancer and paraneoplastic encephalomyelitis or sensory neuropathy, but 13% of these patients have pure or predominant cerebellar findings at presentation (Dalmau *et al*., 1992*b*).

Almost one-half (44%) of patients with small-cell lung cancer and paraneoplastic cerebellar degeneration harbour high titres of HuAb. This antibody when present in high concentration defines a subset of patients different from the seronegative cohort; HuAb positive patients are more likely to be women, have multifocal neurological disease (with brainstem encephalopathy and sensory neuropathy especially common), and be severely disabled. A similar association between the presence of high-titre HuAb and development of multifocal neurological disease has been found in small-cell lung cancer patients with symptom presentation of paraneoplastic limbic encephalitis (Alamowitch *et al*., 1997). Previous American series suggested that paraneoplastic neurological symptoms associated with HuAb affect women more than men (Dalmau *et al*., 1992*b*), but the high prevalence of men with HuAb negative paraneoplastic cerebellar degeneration has not been reported.

Extracerebellar symptoms with paraneoplastic cerebellar degeneration were noted by Greenfield (1934) and Brain *et al*. (1951), and emphasized by Brain and Wilkinson (1965), who found that 21% of their paraneoplastic cerebellar degeneration patients had early sensory symptoms (usually with pain) and other abnormalities, including dementia, muscular weakness, dysphagia, nystagmus and abnormal reflexes. These investigators recognized that diplopia without evidence of ocular paralysis, was a frequent symptom of paraneoplastic cerebellar degeneration. Brain *et al*. (1951), in discussing diplopia stated that 'Its occurrence in cortical cerebellar degeneration is not so unusual as textbook descriptions of the disease would suggest' and they added that, in most cases, it '. . . appears to have been due to lack of balance rather than to paralysis of eye muscles.' In some of our patients with signs of brainstem encephalopathy, we attributed the diplopia to brainstem dysfunction; in others, the diplopia was clearly attributable to Lambert–Eaton myasthenic syndrome (O'Neill *et al*., 1988), but there were patients with isolated and persistent diplopia, the cause of which was either paraneoplastic cerebellar degeneration or uncertain. Diplopia is also a common finding in patients with anti-Yo associated paraneoplastic cerebellar degeneration and ovarian or breast cancer, where pathological changes in brainstem and Lambert–Eaton myasthenic syndrome are rare (Hammack *et al*., 1990; Peterson *et al*., 1992).

CT and MRI imaging are important complementary studies to rule out other neurological complications of cancer, but they are normal or non-specific in the early stages of paraneoplastic cerebellar degeneration (Peterson *et al*., 1992; Posner, 1995). Cerebellar atrophy, if present, occurs months after the neurological symptoms have stabilized. Even in patients with HuAb and encephalomyelitis, the MRI is usually normal (Dalmau *et al*., 1992*b*). Exceptions may occur if there is limbic encephalopathy, in which case, abnormal contrast enhancement or T_2-weighted abnormalities may be found in the medial aspect of the temporal lobes (Dirr *et al*., 1990; Lacomis *et al*., 1990; Dalmau *et al*., 1992*b*), such as occurred in two of our patients.

Similarly, although inflammatory changes (pleocytosis or increased proteins) were identified in 87% HuAb positive and 59% HuAb negative paraneoplastic cerebellar degeneration patients, these abnormalities did not permit differentiation between groups. As previously reported, CSF studies in paraneoplastic disorders are used mainly to rule out leptomeningeal metastases and not to demonstrate antineuronal antibodies which, if present, are always detectable in serum (Graus *et al*., 1988, 1994; Furneaux *et al*., 1990; Dalmau *et al*., 1992*b*) (data not shown). CSF pleocytosis, although

not specific, should increase the clinical suspicion of a paraneoplastic disorder (Dalmau and Posner, 1996).

In most of our patients cerebellar symptoms stabilized spontaneously, leaving the patient substantially incapacitated. Although minor fluctuations in clinical symptoms were observed in a few patients, spontaneous remission is not a feature of this syndrome. Attempts to alleviate the severity of the cerebellar disorder, or halt its progression with a variety of immunomodulating interventions including corticosteroids, plasma exchange, and intravenous gammaglobulin were unsuccessful. Furthermore, efforts directed at controlling the underlying carcinoma, although often successful, had no significant impact on the course or severity of the paraneoplastic cerebellar degeneration.

Among the 37 patients who had evaluable treatment responses, only four had mild improvement of the cerebellar syndrome. Yet, two of these four patients had Lambert–Eaton myasthenic syndrome that dramatically responded to treatment, as has been documented in other Lambert–Eaton myasthenic syndrome cases (Chalk *et al*., 1990). This differential response to treatment of paraneoplastic syndromes of the CNS and Lambert–Eaton myasthenic syndrome has been previously reported (Blumenfeld *et al*., 1991; Fueyo *et al*., 1993; Goldstein *et al*., 1994). The poor response of paraneoplastic cerebellar degeneration to therapy is consistent with our impression, and that of others (Henson and Urich, 1982; Dalmau *et al*., 1992*b*; Graus *et al*., 1992; Uchuya *et al*., 1996), that paraneoplastic disorders of the CNS, particularly when associated with small-cell lung cancer or HuAb, rarely respond to treatment. However, individual case reports describe responses to various treatments of most paraneoplastic syndromes of the CNS (Satoyoshi *et al*., 1973; Paone and Jeyasingham, 1980; Brennan and Craddock, 1983; Cocconi *et al*., 1985; Burton *et al*., 1988; Batson *et al*., 1992; Counsell *et al*., 1994; Antoine *et al*., 1995; Cher *et al*., 1995; Stark *et al*., 1995). In these reports, the underlying tumours are rarely small-cell lung cancer, and the paraneoplastic disorders are usually limbic encephalopathy and opsoclonus, which may improve spontaneously even when the tumour is small-cell lung cancer (Alamowitch *et al*., 1997).

Our patients usually had tumours confined to the thorax at diagnosis. This may represent an anticipation phenomenon, where the development of the neurological disorder, particularly in association with antineuronal antibodies, prompts an investigation for an occult malignancy. Although complete tumour responses were more frequently observed in the HuAb negative patients, the tumours of the HuAb positive patients remained limited during the course of the disease more often than those without HuAb. A larger number of paraneoplastic cerebellar degeneration patients is needed to demonstrate if this less aggressive tumour behavior results from an anti-tumour effect of the HuAb immune response. A similar clinical impression has been obtained from studies of small-cell lung cancer patients without paraneoplastic symptoms but with low titre of HuAb (Dalmau *et al*., 1990); these patients are more likely to be female, have limited disease, and survive longer than patients without HuAb (Graus *et al*., 1996).

Despite limited stage and less aggressive tumour behavior in the HuAb positive group, these patients had significantly shorter life expectancies than small-cell lung cancer patients without paraneoplastic cerebellar degeneration, and death usually occurred as a consequence of the neurological disease. By contrast, patients with paraneoplastic cerebellar degeneration, but without HuAb, were likely to die from the tumour. Yet, for these patients also, survival was significantly shorter than that of neurologically intact small-cell lung cancer controls, and not substantively different from that of HuAb positive patients. None of the paraneoplastic cerebellar degeneration patients without HuAb required ventilation or developed severe dysphagia and autonomic dysfunction, but compared with patients without neurological symptoms, paraneoplastic cerebellar degeneration patients had a lower performance status, which is known to be a poor prognostic factor in small-cell lung cancer (Spiegelman *et al*., 1989; Lassen *et al*., 1995; Rosenfeld *et al*., 1997).

Two of the three patients (cases 1 and 2) described in detail by Brain and Wilkinson (1965) in their series of 19 patients with ‘subacute cerebellar degeneration associated with neoplasms’ may have had Lambert–Eaton myasthenic syndrome. Both patients, in addition to cerebellar ataxia, had mild cranial nerve dysfunction (diplopia, ptosis and facial weakness), proximal weakness of the lower limbs and decreased or absent reflexes. The resemblance of case 1 to a myasthenic syndrome is supported by the treatment that these authors used, including Neostigmine and Mestinon (with partial response to the first and unknown response to the latter); case 2 developed sluggish pupillary responses to light, and ‘under anaesthetic he was extremely sensitive to muscle relaxants’. Considering the limitations of our diagnostic interpretation, these two patients represented 20% of those with lung cancer in the series of Brain and Wilkinson, similar to the frequency of Lambert–Eaton myasthenic syndrome associated with paraneoplastic cerebellar degeneration in our cohort of patients.

Clouston *et al*. (1992) reported on nine patients with a pancerebellar syndrome, six of whom had Lambert–Eaton myasthenic syndrome and one of whom had increased voltage-gated calcium channel antibodies without Lambert–Eaton myasthenic syndrome. In two patients, Lambert–Eaton myasthenic syndrome was discovered only by neurophysiological testing. These authors identified 23 previously reported patients with Lambert–Eaton myasthenic syndrome and paraneoplastic cerebellar degeneration, most of them with lung cancer. They concluded that the frequency of association of paraneoplastic cerebellar degeneration and Lambert–Eaton myasthenic syndrome was higher than expected by chance and that the presence of voltage-gated calcium channel antibodies was not always confined to Lambert–Eaton myasthenic syndrome (Clouston *et al*., 1992). Since then, a new immunoprecipitation assay has been reported by Motomura *et al*. (1995) for detecting antibodies to

voltage-gated calcium channel in Lambert–Eaton myasthenic syndrome using ^{125}I-ω-CmTx, which binds to P/Q-type voltage-gated calcium channel. These antibodies were found in 85% of 66 serum samples from Lambert–Eaton myasthenic syndrome patients and were absent in 10 healthy and 40 disease control patients. Although there is agreement that most Lambert–Eaton myasthenic syndrome patients harbour P/Q-type voltage-gated calcium channel antibodies, another study (Lennon *et al*., 1995) identified similar antibodies in a mixed assortment of patients with different types of cancer either without or with paraneoplastic symptoms or antineuronal antibodies. However, the clinical characterization of these neurological syndromes, the association with specific types of tumours and the co-existence of Lambert–Eaton myasthenic syndrome were not reported.

In patients with small-cell lung cancer, Lambert–Eaton myasthenic syndrome appears to segregate with paraneoplastic cerebellar degeneration, and is usually detectable when symptoms of paraneoplastic cerebellar degeneration emerge. In support of the earlier studies (Satoyoshi *et al*., 1973; Clouston *et al*., 1992; Goldstein *et al*., 1994) suggesting an association between paraneoplastic cerebellar degeneration and Lambert–Eaton myasthenic syndrome, 16% of our patients had Lambert–Eaton myasthenic syndrome. Furthermore, the fact that 24% of small-cell lung cancer patients with paraneoplastic cerebellar degeneration had P/Q-type voltage-gated calcium channel antibodies, and that most patients did not have routine electrophysiological testing, suggest that the real prevalence of Lambert–Eaton myasthenic syndrome is under-represented. The prevalence of P/Q- and N-type voltage-gated calcium channel antibodies is so high in HuAb negative paraneoplastic cerebellar degeneration patients (36% and 29%, respectively) as to suggest that these antibodies may have a role in the pathogenesis of the cerebellar dysfunction. This possibility is supported by the recent discovery that dysfunction of a brain-specific P/Q type voltage-gated calcium channel secondary to mutations in the α1-subunit, results in ataxia (Ophoff *et al*., 1996).

With the exception of the series of Brain and Wilkinson (1965), the lack of other studies focusing on small-cell lung cancer and paraneoplastic cerebellar degeneration may explain that the frequent association with Lambert–Eaton myasthenic syndrome, although suspected, has not been defined until now. It is possible that this association is not restricted to paraneoplastic cerebellar degeneration, and that small-cell lung cancer patients with paraneoplastic encephalomyelitis and sensory neuropathy also have an increased incidence of Lambert–Eaton myasthenic syndrome. Often patients with paraneoplastic encephalomyelitis and sensory neuropathy who present with extracerebellar symptoms have early and severe sensory deficits, brainstem encephalopathy, autonomic dysfunction or lower motor neuron deficits (Dalmau *et al*., 1992*b*), that make the detection of Lambert–Eaton myasthenic syndrome more difficult than in those who present with paraneoplastic cerebellar degeneration alone. Identification of Lambert–Eaton myasthenic syndrome is important because the motor weakness increases the deficits of paraneoplastic cerebellar degeneration or paraneoplastic encephalomyelitis, and because Lambert–Eaton myasthenic syndrome responds to therapy (Newsom-Davis and Murray, 1984; Chalk *et al*., 1990; Blumenfeld *et al*., 1991; Bain *et al*., 1996).

The neuropathological findings of five paraneoplastic cerebellar degeneration patients with a high titre of HuAb are consistent with the protean clinical manifestations of the disorder; i.e. multifocal inflammatory infiltrates in cerebellum, brainstem, and dorsal nerve root and ganglia, along with variable gliosis, loss of neurons and secondary degeneration of the posterior columns of the spinal cord. The extensive loss of Purkinje cells in four of these patients explained the cerebellar findings; however, one patient with brainstem encephalitis (autopsy 3) characterized by opsoclonus and cerebellar signs had no significant loss of Purkinje cells. The pathological findings of the HuAb positive patients are characteristic of 'encephalomyelitis associated with cancer' (Henson *et al*., 1965) rather than a pure cortical cerebellar degeneration (Henson and Urich, 1982).

The case 2 of Greenfield (1934) and cases 3 and 4 of Brain *et al*. (1951) are probably the first reported lung cancer patients with paraneoplastic cerebellar degeneration as a fragment of encephalomyelitis; these patients developed sensory symptoms associated with paraneoplastic cerebellar degeneration, and pathological findings of encephalomyelitis, cerebellar degeneration, dorsal root ganglionitis or degeneration of posterior columns of the spinal cord. Brain *et al*. (1951), in discussing the sensory deficits and pain of their patient 4 stated that 'this symptom, as well as the degeneration of the dorsal columns when it occurs, links these cases with those of polyneuritis associated with carcinoma described by Denny-Brown' (Denny-Brown, 1948).

In contrast to the encephalomyelitis of the HuAb positive patients, no inflammatory infiltrates were identified in the cerebrum, brainstem, cerebellum and spinal cord of two paraneoplastic cerebellar degeneration patients without HuAb (autopsies 7 and 8). The absence of inflammatory infiltrates in these patients may have three explanations. (i) It could represent a burnt-out stage of the same inflammatory mechanism that affects patients with HuAb. This possibility seems unlikely because the interval from neurological symptoms to death was similar to that found in patients with HuAb. (ii) It could represent a different and non-inflammatory pathogenesis, similar to that reported in some patients with Hodgkin's lymphoma, and cancer of the ovary and breast (Peterson *et al*., 1992; Sindic *et al*., 1993; Verschuuren *et al*., 1996), or (iii) it could represent a short-lasting inflammatory disorder more limited and less maintained than that associated with HuAb. We favour this last possibility, because the CSF of one of these patients had inflammatory changes in the early stages of the disease, and because a third patient without HuAb (autopsy 6), who died within 1 month of the course of the disease, had inflammatory infiltrates in the neuraxis (milder and more limited than those affecting HuAb positive

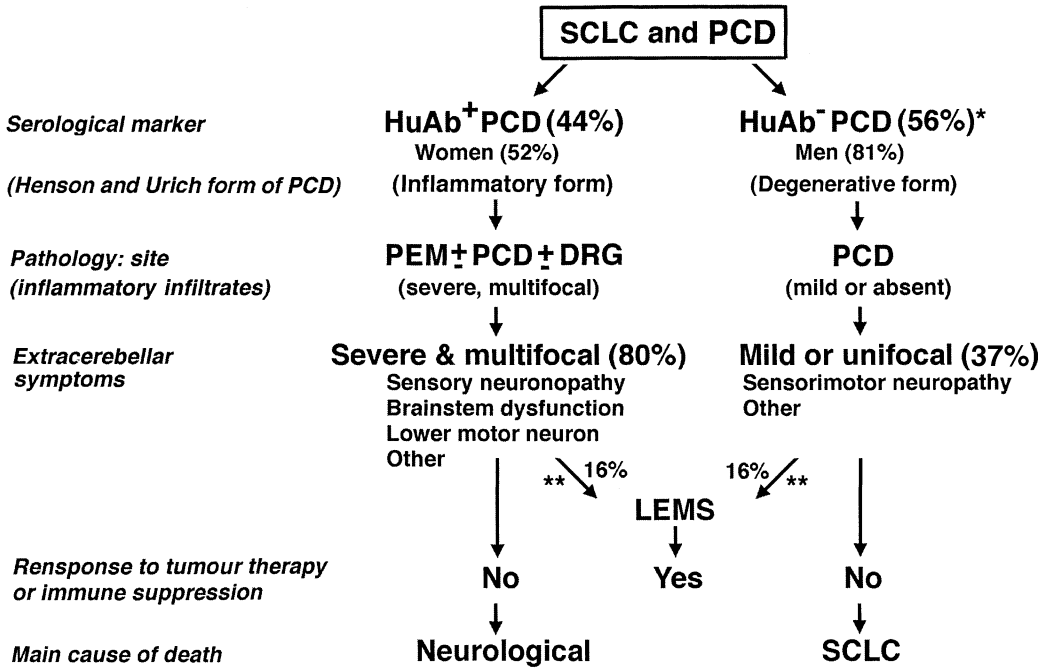

Fig. 6 Paraneoplastic cerebellar degeneration in patients with small-cell lung cancer. Correlations between the Henson and Urich's (pathological) classification of paraneoplastic cerebellar degeneration (PCD) and the HuAb serological classification of paraneoplastic cerebellar degeneration in small-cell lung cancer (SCLC) patients. $HuAb^{+}PCD$ = paraneoplastic cerebellar degeneration and high titres of HuAb; $HuAb^{-}PCD$ = paraneoplastic cerebellar degeneration without HuAb or with low titres of HuAb; PEM = paraneoplastic encephalomyelitis; DRG = dorsal root ganglion. *May represent several disorders; **probably under-represented.

patients) and extensive inflammatory infiltrates in the meninges and CSF. A similar dissociation between the presence of pleocytosis and mild or absent inflammatory infiltrates in the neuraxis was noted by Brain *et al*. (1951), referring to a patient reported by Munch-Petersen in 1947, and by Julien *et al*. (1972).

Our findings support the concepts and classification of cortical cerebellar degeneration proposed by Henson and Urich (1982). In a review of 44 pathologically reported cases of paraneoplastic cerebellar degeneration, these authors differentiated between those with absent or mild inflammation of the neuraxis (27 patients; 33% lung cancer) and those with prominent inflammation (17 patients; 47% lung cancer). To explain these pathological differences they outlined three possibilities: (i) the two groups are morphologically and pathogenetically separate entities; (ii) the second group represents the coexistence of two seemingly independent processes, one degenerative, the other inflammatory or (iii) both groups are variants of a single entity with active inflammation in some cases, burnt out in others. Henson and Urich (1982) considered that the evidence was insufficient to support any of their three views and, therefore, preferred 'to keep an open mind and adhere to strictly morphological classification' (Henson and Urich, 1982). However, the occurrence in some patients of Purkinje cell degeneration independently of encephalomyelitis, or the reverse situation, led Vick *et al*. (1969) to suggest that encephalomyelitis and degeneration of Purkinje cells develop by different and independent mechanisms.

Although there appears to be a strong correlation between our serological classification of paraneoplastic cerebellar degeneration and the morphological classification of Vick *et al*. (1969) and Henson and Urich (1982), this correlation is not perfect. Our study suggests that the pathological substrate of paraneoplastic cerebellar degeneration associated with HuAb corresponds to the 'encephalomyelitic form' of paraneoplastic cerebellar degeneration, and adds serological evidence that this entity is different from paraneoplastic cerebellar degeneration without HuAb. This second group, probably comprise several types of cerebellar degeneration, some without inflammatory mechanisms ('degenerative form of Henson and Urich'), and some with inflammation only detectable in the early stages of the disease. A possible example of this latter group is case 1 of Brain and Wilkinson (1965), considered by Henson and Urich (1982) to be a 'degenerative' form of paraneoplastic cerebellar degeneration, but whose autopsy showed perivascular cuffing only in some vessels of the left amygdaloid nucleus. Another example is our autopsy 6. This patient not only differed pathologically but also serologically from the other two HuAb negative patients with post-mortem studies, since his serum harboured an antibody (CV2) reported in some cases of paraneoplastic encephalitis (Antoine *et al*., 1993; Honnorat *et al*., 1996).

Our views of paraneoplastic cerebellar degeneration in

patients with small-cell lung cancer, supported by this and previous studies (Clouston *et al*., 1992; Dalmau *et al*., 1992*b*), are shown in Fig. 6, and are summarized as follows. (i) The subacute development of a cerebellar syndrome of unknown cause in adult patients, should raise the suspicion of a paraneoplastic disorder, and the serum should be examined for paraneoplastic antibodies; if CSF pleocytosis is present the suspicion is even greater. (ii) In patients without known cancer, the detection of HuAb should prompt a search for small-cell lung cancer. However, the absence of this antibody does not exclude the possibility that the patient may have this type of tumour, since 56% of small-cell lung cancer with paraneoplastic cerebellar degeneration do not develop HuAb. (iii) The detection of high-titre HuAb ($> 1 : 10\,000$) indicates that paraneoplastic cerebellar degeneration is a clinical manifestation of paraneoplastic encephalomyelitis associated (but not always) with cerebellar degeneration, and that the patient will probably develop other neurological symptoms, mainly PSN and brainstem dysfunction. (iv) The absence of HuAb suggests that paraneoplastic cerebellar degeneration results from disorders more confined to cerebellum (i.e. cortical cerebellar degeneration) than paraneoplastic encephalomyelitis, and that symptoms will probably remain restricted to cerebellum or moderately affect other areas of the nervous system. (v) In most patients, treatment of the tumour, paraneoplastic cerebellar degeneration, or both, does not appear to modify the course of the cerebellar disorder. (vi) Regardless of the antibody status, all small-cell lung cancer patients with paraneoplastic cerebellar degeneration, should be examined for Lambert–Eaton myasthenic syndrome. (vii) If Lambert–Eaton myasthenic syndrome is detected, treatment of the tumour may result in neurological improvement, and plasma exchange or intravenous gammaglobulin should be considered, since these therapies may also be effective. (viii) Some paraneoplastic cerebellar degeneration patients without HuAb may harbour voltage-gated calcium channel antibodies without signs of Lambert–Eaton myasthenic syndrome. The high prevalence of voltage-gated calcium channel antibodies in this subset of patients suggests that they may play a role in the pathogenesis of paraneoplastic cerebellar degeneration; thus, regardless of the absence of Lambert–Eaton myasthenic syndrome, plasma exchange may be warranted in these patients.

Acknowledgements

We wish to thank Dr Marc Kris and Dr Stefan Grant, Department of Medicine, Memorial Sloan-Kettering Cancer Center for providing clinical information and sera of patients with small-cell lung cancer.We also wish to thank the following physicians for providing detailed clinical information on patients included in this study: Steven Sugarman, Stony Brook, NY; David Dine, Portland, Oreg.; Lisa Rogers, Detroit, Mich.; Felix Tyndel, Toronto, Canada; Robert Albright, Durham, NC; Richard A. Brodkin, Winston-Salem, NC; Thomas F. Scott, Pittsburgh, Pa.; S. Clifford Schold, Dallas, Tex.; Hiroshi Mitsumoto, Cleveland, OH; Rajeev Motiwala, Hackensack, NJ; Patrick Wen, Boston, Mass.; Hans-Peter Hartung, Würzburg (Germany); Gianpaolo P. Pizzolato, Geneva (Switzerland); Julio Pascual, Santander; Maria José Vila, Cadiz; Carlos Leno, Santander; Antonio Dávalos, Girona; Adriá Arboix, Barcelona; Xavier Montalbán, Barcelona; José Antonio Villanueva, Madrid; Jaime Gallego, Pamplona (Spain). This study was supported in part by grants: NS 26064 (J.B.P. and J.D.); CDA 94–18 (J.D.); FIS 95:0233 and Catalan Society of Neurology, Fundació Uriach (F.G.); The MRC Programme Grant (J.N.D. and B.L.) and the Sir Jules Thorn Charitable Trust (B.L.); INSERM U 433 (J.C.A. and J.H.); INSERM U 134 (J.-Y.D.). F.V. was a recipient of a post-residency grant from the Hospital Clínic.

References

Alamowitch S, Graus F, Uchuya M, Reñé R, Bescansa E, Delattre JY. Limbic encephalitis and small cell lung cancer: clinical and immunological features. Brain 1997. In press.

Anderson NE, Rosenblum MK, Graus F, Wiley RG, Posner JB. Autoantibodies in paraneoplastic syndromes associated with small-cell lung cancer. Neurology 1988; 38: 1391–8.

Antoine JC, Honnorat J, Vocanson C, Koenig F, Aguera M, Belin MF, et al. Posterior uveitis, paraneoplastic encephalomyelitis and auto-antibodies reacting with developmental protein of brain and retina. J Neurol Sci 1993; 117: 215–23.

Antoine JC, Honnorat J, Anterion CT, Aguera M, Absi L, Fournel P, et al. Limbic encephalitis and immunological perturbations in two patients with thymoma. J Neurol Neurosurg Psychiatry 1995; 58: 706–10.

Bain PG, Motomura M, Newsom-Davis J, Misbah SA, Chapel HM, Lee ML, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology 1996; 47: 678–83.

Batson OA, Fantle DM, Stewart JA. Paraneoplastic encephalomyelitis. Dramatic response to chemotherapy alone. Cancer 1992; 69: 1291–3.

Blumenfeld AM, Recht LD, Chad DA, DeGirolami U, Griffin T, Jaeckle KA. Coexistence of Lambert-Eaton myasthenic syndrome and subacute cerebellar degeneration: Differential effects of treatment [see comments]. Neurology 1991; 41: 1682–5. Comment in: Neurology 1992; 42: 1429.

Brain WR, Wilkinson M. Subacute cerebellar degeneration associated with neoplasms. Brain 1965; 88: 465–78.

Brain WR, Daniel PM, Greenfield JG. Subacute cortical cerebellar degeneration and its relation to carcinoma. J Neurol Neurosurg Psychiatry 1951; 14: 59–75.

Brennan LV, Craddock PR. Limbic encephalopathy as a nonmetastatic complication of oat cell lung cancer. Its reversal after treatment of the primary lung lesion. Am J Med 1983; 75: 518–20.

Burton GV, Bullard DE, Walther PJ, Burger PC. Paraneoplastic

limbic encephalopathy with testicular carcinoma. A reversible neurologic syndrome. Cancer 1988; 62: 2248–51.

Chalk CH, Murray NM, Newsom-Davis J, O'Neill JH, Spiro SG. Response of the Lambert-Eaton myasthenic syndrome to treatment of associated small-cell lung carcinoma. Neurology 1990; 40: 1552–6.

Cher LM, Hochberg FH, Teruya J, Nitschke M, Valenzuela RF, Schmahmann JD, et al. Therapy for paraneoplastic neurologic syndromes in six patients with protein A column immunoadsorption. Cancer 1995; 75: 1678–83.

Clouston PD, Saper CB, Arbizu T, Johnston I, Lang B, Newsom-Davis J, et al. Paraneoplastic cerebellar degeneration. III. Cerebellar degeneration, cancer, and the Lambert-Eaton myasthenic syndrome. [Review]. Neurology 1992; 42: 1944–50.

Cocconi G, Ceci G, Juvarra G, Minopoli MR, Cocchi T, Fiaccadori F, et al. Successful treatment of subacute cerebellar degeneration in ovarian carcinoma with plasmapheresis. A case report. Cancer 1985; 56: 2318–20.

Counsell CE, McLeod M, Grant R. Reversal of subacute paraneoplastic cerebellar syndrome with intravenous immunoglobulin. Neurology 1994; 44: 1184–5.

Dalmau J, Graus F. Paraneoplastic Syndromes. In: Samuels MA and Feske S, editors. Office practice of neurology. New York: Churchill Livingstone 1995, 925–34.

Dalmau J, Posner JB. Neurological paraneoplastic syndromes. Springer Semin Immunopathol 1996; 18: 85–95.

Dalmau J, Rosenfeld MR. Characterization of neuronal antigens and antineuronal antibodies. In: Phillips MI, Evans D, editors. Methods in neurosciences, Vol. 24. Neuroimmunology. San Diego: Academic Press, 1995: 261–71.

Dalmau J, Furneaux HM, Gralla RJ, Kris MG, Posner JB. Detection of the anti-Hu antibody in the serum of patients with small cell lung cancer–a quantitative western blot analysis. Ann Neurol 1990; 27: 544–52.

Dalmau J, Furneaux HM, Rosenblum MK, Graus F, Posner JB. Detection of the anti-Hu antibody in specific regions of the nervous system and tumor from patients with paraneoplastic encephalomyelitis/sensory neuronopathy. Neurology 1991; 41: 1757–64.

Dalmau J, Furneaux HM, Cordon-Cardo C, Posner JB. The expression of the Hu (paraneoplastic encephalomyelitis/sensory neuronopathy) antigen in human normal and tumor tissues. Am J Pathol 1992a; 141: 881–6.

Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. Medicine (Baltimore) 1992b; 71: 59–72.

Dalmau J, Graus F, Cheung NK, Rosenblum MK, Ho A, Cañete A, et al. Major histocompatibility proteins, anti-Hu antibodies, and paraneoplastic encephalomyelitis in neuroblastoma and small cell lung cancer. Cancer 1995; 75: 99–109.

Denny-Brown D. Primary sensory neuropathy with muscular changes associated with carcinoma. J Neurol Neurosurg Psychiatry 1948; 11: 73–87.

Dirr LY, Elster AD, Donofrio PD, Smith M. Evolution of brain MRI abnormalities in limbic encephalitis. Neurology 1990; 40: 1304–6.

Fueyo J, Goméz-Manzano C, Pascual J, Pou A. Paraneoplastic syndromes [letter]. Neurology 1993; 43: 236

Furneaux HF, Reich L, Posner JB. Autoantibody synthesis in the central nervous system of patients with paraneoplastic syndromes. Neurology 1990; 40: 1085–91.

Goldstein JM, Waxman SG, Vollmer TL, Lang B, Johnston I, Newsom-Davis J. Subacute cerebellar degeneration and Lambert-Eaton myasthenic syndrome associated with antibodies to voltage-gated calcium channels: differential effect of immunosuppressive therapy on central and peripheral defects [letter]. J Neurol Neurosurg Psychiatry 1994; 57: 1138–9.

González del Val R, García Arroyo R, Villanueva JA, Moro E, Pérez Manga G, García Gómez R. Degeneración subaguda cerebelosa paraneoplásica en el carcinoma microcítico de pulmón. Presentación de dos casos. Med Clin (Barc) 1992; 99: 701–4.

Graus F, Cordon-Cardo C, Posner JB. Neuronal antinuclear antibody in sensory neuronopathy from lung cancer. Neurology 1985; 35: 538–43.

Graus F, Elkon KB, Cordon-Cardo C, Posner JB. Sensory neuronopathy and small cell lung cancer. Antineuronal antibody that also reacts with the tumor. Am J Med 1986; 80: 45–52.

Graus F, Elkon KB, Lloberes P, Ribalta T, Torres A, Ussetti P, et al. Neuronal antinuclear antibody (anti-Hu) in paraneoplastic encephalomyelitis simulating acute polyneuritis. Acta Neurol Scand 1987; 75: 249–52.

Graus F, Segurado OG, Tolosa E. Selective concentration of anti-Purkinje cell antibody in the CSF of two patients with paraneoplastic cerebellar degeneration. Acta Neurol Scand 1988; 78: 210–3.

Graus F, Vega F, Delattre J-Y, Bonaventura I, Reñé R, Arbaiza D, et al. Plasmapheresis and antineoplastic treatment in CNS paraneoplastic syndromes with antineuronal autoantibodies. Neurology 1992; 42: 536–40.

Graus F, Bonaventura I, Uchuya M, Valls-Solé J, Reñé R, Leger JM, et al. Indolent anti-Hu-associated paraneoplastic sensory neuropathy. Neurology 1994; 44: 2258–61.

Graus F, Dalmau J, Reñé R, Torá M, Malats N, Verschuuren JJ, et al. Anti-Hu antibodies in patients with small cell lung cancer: Association with complete response to therapy and improved survival [abstract]. J Neurooncol 1996; 30: 129.

Greenfield JG. Subacute spino-cerebellar degeneration occurring in elderly patients. Brain 1934; 57: 161–76.

Greenlee JE, Brashear HR. Antibodies to cerebellar Purkinje cells in patients with paraneoplastic cerebellar degeneration and ovarian carcinoma. Ann Neurol 1983; 14: 609–13.

Hammack JE, Kimmel DW, O'Neill BP, Lennon VA. Paraneoplastic cerebellar degeneration: a clinical comparison of patients with and

without Purkinje cell cytoplasmic antibodies. Mayo Clin Proc 1990; 65: 1423–31.

Heidenreich F, Schober R, Brinck U, Hartung HP. Multiple paraneoplastic syndromes in a patient with antibodies to neuronal nucleoproteins (anti-Hu). J Neurol 1995; 242: 210–6.

Henson RA, Urich H. Cortical cerebellar degeneration. In: Henson RA and Urich H, editors. Cancer and the nervous system. Oxford: Blackwell Scientific Publications, 1982: 346–67.

Henson RA, Hoffman HL, Urich H. Encephalomyelitis with carcinoma. Brain 1965; 88: 449–64.

Hersh B, Dalmau J, Dangond F, Gultekin S, Geller E, Wen PY. Paraneoplastic opsoclonus-myoclonus associated with anti-Hu antibody [see comments]. Neurology 1994; 44: 1754–5. Comment in: Neurology 1995; 45: 1421–2.

Hetzel DJ, Stanhope CR, O'Neill BP, Lennon VA. Gynecologic cancer in patients with subacute cerebellar degeneration predicted by anti-Purkinje cell antibodies and limited in metastatic volume. Mayo Clin Proc 1990; 65: 1558–63.

Honnorat J, Antoine JC, Derrington E, Aguera M, Belin MF. Antibodies to a subpopulation of glial cells and a 66 kDa developmental protein in patients with paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 1996; 61: 270–8.

Jaeckle KA, Graus F, Houghton A, Cardon-Cardo C, Nielsen SL, Posner JB. Autoimmune response of patients with para-neoplastic cerebellar degeneration to a Purkinje cell cytoplasmic protein antigen. Ann Neurol 1985; 18: 592–600.

Julien J, Vital C, Vallat JM. Atrophie cérébelleuse paranéoplasique. Observation anatomo-clinique. Bord Méd 1972; 5: 2461–7.

Kiers L, Altermatt HJ, Lennon VA. Paraneoplastic anti-neuronal nuclear IgG autoantibodies (type I) localize antigen in small cell lung carcinoma. Mayo Clin Proc 1991; 66: 1209–16.

Lacomis D, Khoshbin S, Schick RM. MR imaging of paraneoplastic limbic encephalitis. J Comput Assist Tomogr 1990; 14: 115–7.

Lassen U, Osterlind K, Hansen M, Dombernowsky P, Bergman B, Hansen HH. Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5 to 18+ years–an analysis of 1,714 consecutive patients. J Clin Oncol 1995; 13: 1215–20.

Lennon VA, Kryzer TJ, Griesmann GE, O'Suilleabhain PE, Windebank AJ, Woppmann A, et al. Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med 1995; 332: 1467–74.

Luque FA, Furneaux HM, Ferziger R, Rosenblum MK, Wray SH, Schold SC, et al. Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. Ann Neurol 1991; 29: 241–51.

Manley GT, Smitt PS, Dalmau J, Posner JB. Hu antigens: reactivity with Hu antibodies, tumor expression, and major immunogenic sites. Ann Neurol 1995; 38: 102–10.

Motomura M, Johnston I, Lang B, Vincent A, Newsom-Davis J. An improved diagnostic assay for Lambert-Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry 1995; 58: 85–7.

Munch-Petersen CJ. Ataxia subacuta atrophia cerebelli primaria. Acta Psychiatrica et Neurologica 1947; 213–25.

Newsom-Davis J, Murray NM. Plasma exchange and immunosuppressive drug treatment in the Lambert-Eaton myasthenic syndrome. Neurology 1984; 34: 480–5.

O'Neill JH, Murray NM, Newsom-Davis J. The Lambert-Eaton myasthenic syndrome. A review of 50 cases. Brain 1988; 111: 577–96.

Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SMG, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 1996; 87: 543–52.

Paone JF, Jeyasingham K. Remission of cerebellar dysfunction after pneumonectomy for bronchogenic carcinoma. N Engl J Med 1980; 302: 156

Peterson K, Rosenblum MK, Kotanides H, Posner JB. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody positive patients. Neurology 1992; 42: 1931–7.

Posner JB. Paraneoplastic syndromes. In: Posner JB. Neurologic complications of cancer. Philadelphia: F.A. Davis, 1995: 353–85.

Rosenfeld MR, Malats N, Schramm L, Graus F, Torá M, Cardenal F, et al. Serum anti-p53 antibodies are not a prognostic marker in small cell lung cancer. J Natl Cancer Inst 1997; 89: 381–5.

Ruigomez A, Alonso J, Anto JM. Relationship of health behaviours to five-year mortality in an elderly cohort. Age Ageing 1995; 24: 113–9.

Satoyoshi E, Kowa H, Fukunaga N. Subacute cerebellar degeneration and Eaton-Lambert syndrome with bronchogenic carcinoma. Neurology 1973; 23: 764–8.

Sindic CJ, Andersson M, Boucquey D, Chalon MP, Bisteau M, Brucher JM, et al. Anti-Purkinje cells antibodies in two cases of paraneoplastic cerebellar degeneration. Acta Neurol Belg 1993; 93: 65–77.

Spiegelman D, Maurer LH, Ware JH, Perry MC, Chahinian AP, Comis R, et al. Prognostic factors in small-cell carcinoma of the lung:an analysis of 1,521 patients. J Clin Oncol 1989; 7: 344–54.

Stark E, Wurster U, Patzold U, Sailer M, Haas J. Immunological and clinical response to immunosuppressive treatment in paraneoplastic cerebellar degeneration. Arch Neurol 1995; 52: 814–8.

Towbin H, Staehelin T, Gordon J. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. Proc Natl Acad Sci USA 1979; 76: 4350–4.

Trotter JL, Hendin BA, Osterland CK. Cerebellar degeneration with Hodgkin disease. An immunological study. Arch Neurol 1976; 33: 660–1.

Uchuya M, Graus F, Vega F, Reñé R, Delattre JY. Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies. J Neurol Neurosurg Psychiatry 1996; 60: 388–92.

Verschuuren J, Chuang L, Rosenblum MK, Lieberman F, Pryor A, Posner JB, et al. Inflammatory infiltrates and complete absence

of Purkinje cells in anti-Yo-associated paraneoplastic cerebellar degeneration. Acta Neuropathol (Berl) 1996; 91: 519–25.

Vick N, Schulman S, Dau P. Carcinomatous cerebellar degeneration, encephalomyelitis, and sensory neuropathy (radiculitis). Report of a case incorporating both purely degenerative and intense inflammatory changes, with special prominence of the latter in the putamen. Neurology 1969; 19: 425–41.

Wilkinson PC, Zeromski J. Immunofluorescent detection of antibodies against neurones in sensory carcinomatous neuropathy. Brain 1965; 88: 529–38.

Received December 12, 1996. Revised March 9, 1997.
Accepted March 17, 1997