Neurological paraneoplastic syndromes in patients with small cell lung cancer. A prospective survey of 150 patients

G M Elrington, N M F Murray, S G Spiro, J Newsom-Davis

Abstract

One hundred and fifty patients presenting with small cell lung cancer (SCLC) to chest physicians, were assessed neurologically. Neuromuscular or autonomic deficits were common and occurred in up to 44% of cases. Weakness, dry mouth, and weight loss were not mutually independent and may represent the syndrome formerly described as carcinomatous neuromyopathy. By contrast, undoubted paraneoplastic syndromes were much less commonly detected. Two patients had the Lambert-Eaton myasthenic syndrome (LEMS) and one had subacute sensory neuropathy (SSN). In these patients, neurological symptoms antedated other manifestations of cancer, by between six and 17 months. The 95% confidence interval for the prevalence of LEMS or SSN among SCLC patients was 0-4%, consistent with the results of previous retrospective or smaller studies: summing these, the overall prevalence of LEMS among SCLC patients is close to 3%, which implies about 250 new cases per annum in England and Wales. If LEMS and SSN are the least uncommon neurological paraneoplastic syndromes in SCLC patients, this may reflect the accessibility of motor nerve terminals and dorsal root ganglia to cross-reactive anti-tumour cell antibodies.

Small cell lung cancer (SCLC) is the tumour most commonly associated with a range of neurological paraneoplastic syndromes; 25% of all patients with lung cancer have this cell type.¹ Henson and Urich² defined syndromes as paraneoplastic if associated with cancer and not due to the presence of cancer in the affected organ. Other tumours are associated with individual paraneoplastic syndromes, such as malignancies of the female genital tract with cerebellar degeneration,³ neuroblastoma with opsoclonus,² and Hodgkin's disease with demyelinating neuropathy.⁴ Such specific associations are also seen with SCLC, but the range of neurological syndromes complicating this common and highly malignant cancer include the Lambert-Eaton myasthenic syndrome (LEMS),⁵ subacute sensory neuropathy (SSN),⁶ myelopathy,⁷ cerebellar degeneration,⁸ and encephalopathy.⁶ These syndromes may coexist.² Opsoclonus,⁹ and

retinal degeneration¹⁰ are also reported, less commonly, in SCLC patients.

The immunopathology of LEMS has recently been reviewed.¹¹ LEMS appears to be caused by the downregulation of presynaptic voltage gated calcium channels (VGCCs), following cross-linking by divalent anti-VGCC IgG antibodies. VGCC are also present in the cell membrane of SCLC, which, in immunogenetically susceptible individuals, may trigger the formation of anti-VGCC antibodies.

The frequency at which paraneoplastic neurological disorders occur in association with SCLC is uncertain, and most data have been obtained in retrospective studies. These syndromes might easily be overlooked, particularly in the case of LEMS,⁵ in patients known to have a malignant neoplasm. We therefore undertook a prospective survey to assess the prevalence of neurological paraneoplastic syndromes among patients with SCLC.

Methods

One hundred and fifty consecutive patients with a tissue diagnosis of SCLC were assessed clinically at five hospitals participating in trials of chemotherapy for SCLC. Mean (SD) age was 64 (7.4) years and 79% were male. Thirty five per cent had limited disease, that is, confined to one hemithorax, or with bilateral hilar involvement. Eighty per cent were recruited to trials of chemotherapy, but all patients were assessed before the administration of cytotoxic drugs. Tissue diagnosis was achieved following fiberoptic bronchoscopy in 122 cases, of which 114 had a positive biopsy; the other eight were diagnosed on cytological examination of bronchial washings. Nine cases were diagnosed by sputum cytology alone, and eleven from other non-bronchoscopic biopsies. All patients had been given a diagnosis of SCLC, but four also had co-existent non-SCLC bronchogenic tumours.

A standard assessment protocol was used. Background information about the presentation of the tumour, and its diagnosis, was established from clinical case notes. Enquiry about past medical history and family history included direct questions about diabetes, thyroid disease, and neurological disease. Current and recent medication was recorded. Direct questions were asked to establish the presence or absence of weakness, anorexia, weight loss, dry mouth, sphincter difficulty, erectile impotence, diplopia, and ptosis. A

**The National Hospital,
London, UK
G M Elrington
NMF Murray
SG Spiro
J Newsom-Davis**

Correspondence to:
Dr Elrington, Department of
Clinical Neurology, Radcliffe
Infirmary, Woodstock Road,
Oxford OX2 6HE, UK

Received 10 September 1990
and in final revised form
8 February 1991.
Accepted 21 February 1991.

detailed neurological assessment was performed, but in 20 cases this was limited by the patient's inability to stand. Tendon reflexes were elicited before assessment of muscle power, and, in subjects with diminished reflexes, again after 15 seconds sustained muscular contraction, in at least two muscles. Cardiovascular reflexes were assessed in a standard manner: the resting, supine blood pressure and heart rate were measured. Patients then stood, and measurements were repeated: standing blood pressure was measured, and heart rate counted, starting 15 to 20 seconds after the patient began to stand.

Patients had electrophysiological testing if a diagnosis of LEMS or another neurological paraneoplastic syndrome was suspected from the clinical assessment (n = 7). To establish a diagnosis of LEMS, the amplitude of the compound muscle action potential (CMAP) was measured in abductor digiti minimi in response to supramaximal stimulation of the ulnar nerve, before and after 15 seconds maximal voluntary contraction. In some cases, the response to trains of stimuli at 5 and 20 Hz was examined, and single fibre electromyography was performed.

Electrophysiological criteria for the diagnosis of LEMS were taken from the data of Newson-Davis and Murray:¹² resting CMAP amplitude <8.4 mV, and increment >25% following 15 seconds maximal voluntary contraction (MVC) being abnormal (% increment = 100 × [amplitude post MVC – initial amplitude] ÷ initial amplitude). These criteria were stringent and would, for example, have excluded two of fifty subjects who were accepted as having LEMS on other grounds, such as a characteristic clinical picture and abnormal single fibre electromyography.⁵

All clinical data were tested for lack of mutual independence, using Chi squared with Yates' correction. For simplicity of expression, features found not to be mutually independent will be referred to as associated. Because multiple comparisons were made, the threshold of significance was set high at p < 0.001.

Results

The frequency of neuromuscular symptoms and signs among the 150 SCLC patients is shown, as a percentage, in table 1. Anorexia and weight loss were the commonest non-respiratory symptoms, followed by dry mouth, and erectile impotence among male subjects (sexual dysfunction was not sought among the female subjects). Physical examination revealed weakness in some subjects who had not complained of this symptom, and overall, 44% had either subjective or objective weakness, or both.

Some symptoms were mutually associated, especially anorexia and weight loss (p < 0.00001), supporting the accuracy of patients' histories. Weight loss was also associated with dry mouth (p < 0.001). All three measures of weakness (symptomatic,

Table 1 Neuromuscular and somatic clinical features of 150 SCLC patients

	% of total
Symptoms:	
Anorexia	53
Weight loss	51
Erectile impotence (males)	44
Dry mouth	41
Weakness ¹	31
Sphincter disturbance	24
Sweating change	21
Visual change	6
Physical signs:	
Unable to rise from squatting position	21
Sensory change	16
Brisk reflexes	13
Absent reflexes	10
Diminished reflexes	9
Weakness ²	8
Ataxia or nystagmus	5
Post tetanic potentiation	3

¹One or more measures of weakness was present in 44% of subjects.
²Excluding inability to rise from squatting position.

objective proximal weakness, and inability to rise from a squatting position) were associated with each other (p < 0.001); symptomatic and proximal weakness were each associated with dry mouth (p < 0.001). These data are shown in the figure.

Other clinical parameters were mutually independent. Abnormal cardiovascular reflexes were common: 11% had a postural systolic blood pressure fall of >29 mmHg, with a borderline fall of 11–29 mmHg in a further 26%.¹³ In 18% of subjects, the pulse rate failed to rise on standing.

LEMS was suspected from the clinical assessment in seven patients. Their details are shown in table 2. Six of these agreed to have EMG studies, and diagnostic features of LEMS were present in two; these two were also distinguished by their long histories of weakness, 11 and 17 months before the diagnosis of SCLC.

One patient had SSN. This 63 year old woman presented with a six month history of painful sensory loss in all four limbs, and also described dry mouth and weakness; examination revealed distal sensory loss to pain, and joint position sense impairment with sensory ataxia. Sensory action potentials were absent from right median, ulnar, radial, and sural nerves; motor conduction velocities were normal. Right ulnar CMAP was slightly reduced, at 7.0 mV, but there was no pathological increment.

Figure Clinical features, for which the null hypothesis that they were mutually independent may be rejected (p < 0.001; Chi squared, with Yates' correction), are shown linked.

Table 2 SCLC patients in whom a diagnosis of LEMS was suspected on clinical grounds

Sex	Length of symptoms (months)	First symptom	Weakness ¹	Dry Mouth ¹	Erectile impotence ² (males)	Tendon reflexes ³	Clinical PTP ⁴	CMAP (mV) ⁵	Increment ⁶ %
F	17	Weakness	++	++		—	++	1.2	610
M	11	Weakness	++	+	+	+	+	2.4	212
F	4	Dry mouth	+++	+++		—	++	Not done	
M	3	Weakness	++	++	+	+	+	15.0	Not done
M	2	Weakness	++	+	+	+	+	4.0	12
F	2	Haemoptysis	+	+++		+	—	10.5	1
M	3	Dyspnoea	+	++	—	+	—	9.5	0

¹Symptoms scored as mild (+), moderate (++) or severe (+++).²Erectile impotence scored as present (+) or absent (—).³Tendon reflexes scored as absent (—), or present without reinforcement (+).⁴Post tetanic potentiation of muscle power or of tendon reflexes; scored as absent (—), barely present (+), or clearly present (++).⁵Amplitude of compound muscle action potential (CMAP); normal > 8.4 mV (12).⁶Increment of CMAP following 15 seconds maximal voluntary contraction; normal < 25% (12).

Twenty four subjects had sensory impairment, most commonly distal vibration sense loss, and 15 were areflexic. These two features were not significantly associated ($0.01 < p < 0.05$).

Four patients had ataxia of the trunk and limbs, of whom two had CT evidence of cerebellar brain metastases. In one case without radiological evidence of metastases, the ataxia was mild, in the other it was of sudden onset with subsequent improvement, and therefore attributed to stroke. Three patients had nystagmus, without ataxia.

In patients with LEMS and SSN, neurological symptoms antedated other manifestations of SCLC, but in none of these three patients was the correct neurological diagnosis suspected before recruitment to this survey. The 95% confidence interval for their combined prevalence was 0–4%.

Four patients presented with symptoms from cerebral metastases, demonstrated on CT brain scan. Their otherwise asymptomatic thoracic lesions were demonstrated by chest radiograph and confirmed histologically. Thus the 95% confidence interval for the prevalence of SCLC presenting with cerebral metastases was 0–5%.

Discussion

In this prospective study of 150 patients presenting with SCLC to chest physicians, three patients (95% confidence interval: 0–4%) presented with neurological paraneoplastic syndromes (two LEMS, one SSN), similar to the number presenting with brain metastases. No patients were thought to have paraneoplastic cerebellar degeneration (PCD), although it could be argued that mild, non-progressive ataxia or nystagmus could represent PCD; but PCD is typically severe and progressive. Hawley *et al*¹⁴ also found no cases of PCD in their survey of 71 SCLC patients.

Autonomic disturbance has been reported as a specific paraneoplastic syndrome,^{15,16} but none of our patients presented with cardiovascular autonomic failure although many complained of dry mouth and of erectile impotence. Postural hypotension was perhaps commoner than might have been expected; subgroup analysis on the basis of other causes of postural hypotension (drugs, diabetes, cardiac disease, or hyponatraemia) suggested that conditions other than SCLC did not account for these findings. On average, rise in standing pulse rate was lower ($p < 0.001$: Student's *t* test) than in a previously reported group of healthy controls of similar age distribution,¹⁷ although the sig-

nificance of this difference fell to $p < 0.01$ when subjects with other sufficient cause of autonomic disturbance were excluded from the analysis.

Dry mouth has been reported as a specific feature of LEMS, useful in the differential diagnosis from myasthenia gravis.⁵ The presence of this symptom in 41% of SCLC patients limits its value in the diagnosis of weakness in patients known to have SCLC.

In this sample of 150 patients, the finding of weakness in 44% of the subjects is likely to be representative of all SCLC patients. The lower incidence of LEMS and of SSN is clearly subject to a large error, and the 95% confidence interval of 0–4% implies that, on these data, any survey of SCLC patients might yield no cases.

The 95% confidence interval could be narrowed by studying a larger sample of SCLC patients; but if our data are representative of all cases of SCLC, a sample size of 1000 SCLC patients would be required to reduce the range of the confidence interval to $\pm 1\%$.

Previous studies have addressed this question, either on a smaller scale or in retrospective series. Lambert's group¹⁸ estimated that LEMS affected 6% of SCLC subjects, on the basis of case findings in an estimated total lung cancer population among whom 16% were thought to have SCLC. This 16% is an underestimate: a review of 449 old pathological specimens found that SCLC had been diagnosed in 7% of all lung cancer patients, but 22% had this cell type according to modern criteria.¹⁹ Lambert's SCLC population was therefore larger than his estimate, thus reducing the apparent prevalence of LEMS in his series, which was also likely to have been influenced by selection bias. It was acknowledged that the 6% figure was a rough estimate, and seemed inconsistent with the data of Balz¹⁸ who studied 29 SCLC patients electrophysiologically and found no cases of LEMS. Similarly, Croft and Wilkinson,²⁰ in a prospective series, found no cases of "myasthenic neuromyopathy" among 319 cases of lung cancer, of whom 25% would have had SCLC.

More recent, prospective studies, have been smaller than our series. An electrophysiological study of 71 SCLC patients detected two cases of LEMS.¹⁴ A clinical study found two cases among 35 patients with SCLC.²⁰ A recent retrospective necropsy series of 85 SCLC patients contained five with LEMS;²² but LEMS patients are more likely to have a necropsy than non-LEMS SCLC patients.

If the present series is added to previous

Table 3 Reported prevalence of LEMS among SCLC patients

Authors	LEMS cases	SCLC population	LEMS prevalence (%)
Lambert <i>et al</i> 1961 ¹⁸	12	328 ¹	4
Balz ²	0	29	0
Croft and Wilkinson 1965 ²⁰	0	80 ^{2,3}	0
Hawley <i>et al</i> 1980 ¹⁴	2	71	3
De la Monte <i>et al</i> 1984 ²²	5	85	6
Gomm 1986 ²¹	2	35	6
Present series	2	150	2
Totals	23	778	3

¹Original report assumes SCLC as 16% of estimated lung cancer population; assumption revised here to 25%—see text for explanation.

²Reported by Lambert *et al*, 1961¹⁸.

³Assuming SCLC as 25% of all 319 cases of lung cancer.

data, then 23 cases of LEMS have been detected among 778 SCLC patients, an overall prevalence of 3%. These figures are shown in table 3.

The annual death rate from all types of lung cancer in England and Wales is 35 000,²³ of whom 25% have SCLC. If 3% of SCLC patients have LEMS, then there will be 262 new cases of SCLC associated LEMS each year. The symptoms of neurological paraneoplastic syndromes typically predate other manifestations of cancer,³ as was also observed in this survey; yet although the survey raised local awareness of the existence of these syndromes, the correct neurological diagnosis was not made until after SCLC was detected. It is likely that the majority of neurological paraneoplastic syndromes escape diagnosis in SCLC patients.

SCLC carries a grave prognosis, which non-SCLC LEMS does not.⁵ There is therefore a selection bias towards non-SCLC LEMS in neurological practice. The ratio of paraneoplastic to non-paraneoplastic LEMS is likely to be greater than the 2:1 ratio previously reported.⁵

Weakness was the single commonest neurological abnormality among these SCLC patients. Weakness, weight loss, and dry mouth were not mutually independent clinical features, perhaps reflecting a common cause. Familiarity with LEMS might suggest that diagnosis in SCLC patients complaining of weakness and dry mouth; but over one third of SCLC subjects were weak, and less than 2% had LEMS. These symptoms were associated with weight loss, which is known to correlate with neurological abnormalities.¹⁴

Before the introduction of the concept of paraneoplastic syndromes, the term "neuromyopathy" was used. This was introduced by Brain and Henson²⁴ to describe dysfunction at any level in the nervous system, in cancer patients. Croft and Wilkinson¹⁹ found evidence of neuromyopathy in 15% of lung cancer patients. Shy and Silverstein²⁵ restricted the term to describe proximal muscle weakness and reduced myotactic reflexes, yet still found it to be the commonest neurological abnormality in cancer patients. The term neuromyopathy is ambiguous implying neither neuropathy nor myopathy, both of which occur in cancer patients, although it has been shown that these changes were more closely related to weight loss than to the presence of cancer.¹⁴ Our data also suggest that weakness in SCLC patients may be a consequence of weight loss.

LEMS and SSN are both associated with antibodies to SCLC antigens which recognise determinants at motor nerve terminals and at

dorsal root ganglia, respectively. Other neurological paraneoplastic syndromes which also associate with crossreactive antibodies were not detected in this survey. The greater frequency of LEMS and SSN among neurological paraneoplastic syndromes may reflect the fact that motor nerve terminals and dorsal root ganglia lack the blood-nerve and blood-brain barriers that may protect other neural antigens.²⁶

GME gratefully acknowledges the support of the Cancer Research Campaign, who also funded the trials of chemotherapy, upon which recruitment to this survey was based.

Preliminary results from this study were presented to the Association of British Neurologists, 27–29 October 1988.

- Ianuzzi MC, Scoggin CH. Small cell lung cancer. *Am Rev Resp Dis*. 1986;134:593–608.
- Henson RA, Urich H. *Cancer and the nervous system*. Oxford: Blackwell Scientific, 1982:311–621.
- Dropcho EJ. The remote effects of cancer on the nervous system. *Neurological clinics*, Vol 7. Philadelphia: WB Saunders, 1989:579–603.
- Lisak RP, Mitchell M, Zweiman B, Asbury AK. Guillain Barré syndrome and Hodgkin's disease; three cases with immunological studies. *Ann Neurol*. 1977;1:72–8.
- O'Neill JH, Murray NMF, Newsom-Davies J. The Lambert-Eaton myasthenic syndrome: a review of 50 cases. *Brain* 1988;111:577–96.
- Graus F, Elkon KB, Cordon-Cardo C, Posner J. Sensory neuropathy and small cell lung cancer: anti-neuronal antibody that also reacts with the tumour. *Am J Med* 1986;80:45–52.
- Babikian VL, Stefansson K, Dieperink ME, Arnason BGW, Marton L, Levy BE. Paraneoplastic myelopathy: antibodies against protein in normal spinalcord and underlying neoplasm. *Lancet* 1985;ii:49–50.
- Greenlee JE, Lipton HL. Anticerebellar antibodies in serum and CSF of a patient with oat cell carcinoma of lung and paraneoplastic cerebellar degeneration. *Ann Neurol* 1986;19:82–85.
- Ridley A, Kennard C, Scholtz CL, Buttner-Ennever JA, Summers B, Turnbull A. Omnipause neurones in two cases of opsoclonus associated with oat cell carcinoma of the lung. *Brain* 1987;110:1699–709.
- Kornguth SE, Kalinke T, Scjutta H, Dahl D. Anti-neurofilament antibodies in the sera of patients with small cell carcinoma of the lung and with visual paraneoplastic syndrome. *Cancer Research* 1986;46:2588–95.
- Vincent A, Lang B, Newsom-Davis J. Autoimmunity to the voltage-gated calcium channel underlies the Lambert-Eaton myasthenic syndrome, a paraneoplastic disorder. *Trends in Neuroscience* 1989;12:496–502.
- Newsom-Davis J, Murray NMF. Plasma exchange and immunosuppressant drug treatment in the Lambert-Eaton myasthenic syndrome. *Neurology* 1984;34:480–5.
- Ewing DJ. Recent advances in the non-invasive investigation of diabetic autonomic neuropathy. In: Bannister R, ed. *Autonomic failure*. Oxford: University Press, 1988: 667–89.
- Hawley RJ, Cohen MH, Saini N, Armbrustmacher VW. The carcinomatous neuromyopathy of oat cell lung cancer. *Ann Neurol*. 1980;7:65–72.
- Park DM, Johnson RH, Crean GP, Robinson JF. Orthostatic hypertension in bronchial carcinoma. *Br M J* 1972;3:510–1.
- Maier HC, Sommers SC. Neuroendocrine carcinoma of lung associated with bradycardia and episodic cardiac asystole. *Ann Thoracic Surgery* 1986;41:560–2.
- Strandell T. Circulatory studies on healthy old men. *Act Med Scand*. 1964;(Suppl) 414:1–44.
- Lambert EH, Rooke ED, Eaton LM, Hodgson CH. Myasthenic syndrome occasionally associated with bronchial neoplasm: neurophysiologic studies. In: Viets HR ed. *Myasthenia gravis*. Springfield: Thomas, 1961:362–410.
- Yesner R, Gelfman NA, Feinstein AR. A reappraisal of histopathology in lung cancer and correlation of cell types with antecedent cigarette smoking. *Am Rev Resp Dis* 1973;107:790–7.
- Croft PB, Wilkinson M. The incidence of carcinomatous neuromyopathy with special reference to lung and breast carcinoma. In: Brain R and Norris FH, eds. *The remote effects of cancer on the nervous system*. New York: Grune and Stratton, 1965:44–54.
- Gomm SA. *Neuromuscular disorders and lung cancer* (Thesis). Manchester: University of Manchester. 1986.
- De la Monte S, Hutchins GM, Moore GW. Paraneoplastic syndromes and constitutional symptoms in prediction of metastatic behaviour of small cell carcinoma of the lung. *Am J Med* 1984;77:851–7.
- Office of Population Censuses and Surveys. 1986 mortality statistics: cause (England and Wales). London: OPCS, 1988:104–5.
- Brain R, Henson RA. Neurological syndromes associated with carcinoma. *Lancet* 1958;ii:971–5.
- Shy GM, Silverstein I. A study of the effects upon the motor unit by remote malignancy. *Brain* 1965;88:515–28.
- Rapoport SI. *Blood-brain barrier in physiology and medicine*. New York: Raven Press, 1976:74–9, 140–2.