Paraneoplastic neurologic disorders in small cell lung carcinoma

A prospective study

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ABSTRACT

Objective: To determine the frequency and range of paraneoplastic neurologic disorders (PNDs) and neuronal antibodies in small cell lung carcinoma (SCLC).

Methods: Two hundred sixty-four consecutive patients with biopsy-proven SCLC were recruited at the time of tumor diagnosis. All patients underwent full neurologic examination. Serum samples were taken prior to chemotherapy and analyzed for 15 neuronal antibodies. Thirty-eight healthy controls were analyzed in parallel.

Results: PNDs were quite prevalent ($n = 24$, 9.4%), most frequently Lambert-Eaton myasthenic syndrome (3.8%), sensory neuronopathy (1.9%), and limbic encephalitis (1.5%). Eighty-seven percent of all patients with PNDs had antibodies to SOX2 (62.5%), HuD (41.7%), or P/Q VGCC (50%), irrespective of their syndrome. Other neuronal antibodies were found at lower frequencies (GABA_B receptor [12.5%] and N-type VGCC [20.8%]) or very rarely (GAD65, amphiphysin, Ri, CRMP5, Ma2, Yo, VGKC complex, CASPR2, LGI1, and NMDA receptor [all <5%]).

Conclusions: The spectrum of PNDs is broader and the frequency is higher than previously appreciated, and selected antibody tests (SOX2, HuD, VGCC) can help determine the presence of an SCLC. *Neurology*® 2015;85:235-239

GLOSSARY

HC = healthy control; **LE** = limbic encephalitis; **LEMS** = Lambert-Eaton myasthenic syndrome; **PCD** = paraneoplastic cerebellar degeneration; **PEM** = paraneoplastic encephalomyelitis; **PND** = paraneoplastic neurologic disorder; **SCLC** = small cell lung carcinoma; **SN** = sensory neuronopathy.

A paraneoplastic neurologic disorder (PND) results from the indirect effect of a tumor on the nervous system or muscle without local invasion or metastasis. PNDs are often associated with antibodies that bind to proteins shared between the tumor and the nervous system.¹ Small cell lung carcinoma (SCLC) is the most common tumor associated with PNDs,² with a UK incidence of 6,000–10,000 per annum.³ SCLC has neuroendocrine characteristics and expresses many neuronal antigens.⁴

Three previous studies were designed to establish the prevalence of PNDs in SCLC; one found 2% PND prevalence (3/150) among patients with SCLC from 5 UK centers,⁵ but no antibodies were measured. The other 2 studies looked exclusively for Lambert-Eaton myasthenic syndrome (LEMS), finding the prevalence of LEMS in SCLC to be 3% (4/148⁶ and 2/63,⁷ respectively). Thus the frequency of the entire range of PNDs and neuronal antibodies in SCLC has not been determined systematically. Furthermore, with the recent discovery of a new category of disorder mediated by autoantibodies against neuronal cell surface proteins such as NMDA receptor and LGI1,⁸ it is important to determine whether these antibodies are present in SCLC PNDs.

By systematically studying an unselected, unbiased SCLC patient cohort from a single region with complete follow-up, we aimed to determine the incidence and range of PNDs in SCLC more precisely. Given that almost half of all PND patients with an identifiable tumor have

Supplemental data
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SCLC,² we believed that this study would give an accurate overall picture of the frequency of PNDs and associated antibodies.

METHODS Patient selection and evaluation. From April 2005 until November 2010 inclusive (66 months), unselected patients with biopsy-proven SCLC who consecutively consented to the study were recruited at time of tumor diagnosis from lung oncology clinics in hospitals within the Trent region of the UK. All patients underwent full neurologic evaluation and examination, and serum samples were taken prior to chemotherapy and stored at -80°C for further analysis. In parallel, patients in the same region with possible PNDs were referred to and evaluated by one of the authors (P.M.) and included in the study if subsequent investigations revealed an associated SCLC. Patients with PNDs were identified according to recommended diagnostic criteria.⁹ Follow-up clinical data were obtained on all patients from medical records. Any patient initially included in the study who subsequently developed new neurologic symptoms was seen again for review. Healthy control (HC) sera were obtained from a biobank of samples donated by consenting volunteers in Nottingham (who had no history of cancer, neurologic disease, or autoimmune disease based on questionnaire responses and on inspection of up-to-date local medical records at the end of the study). The 38 HC volunteers were selected to age-match a cross-section of the SCLC cohort and included 34% heavy smokers (≥ 15 pack-year history).

Standard protocol approvals, registrations, and patient consents. The regional ethics committee approved the use of human participants for this study (Nottingham REC approval no. 04/Q2404/100). Written informed consent was obtained from all participating patients and HC volunteers.

Serology. The sera were analyzed in parallel with routine diagnostic samples in a blinded manner. Commercial immunoblotting was used for antibodies to recombinant HuD, Yo, Ri, CRMP5, amphiphysin, and Ma2 (RAVO Diagnostika, Freiburg, Germany), with samples diluted 1:2,000. VGCC, VGKC complex, and GAD65 antibodies were detected by radioimmunoprecipitation assays.^{10–12} SOX2 antibodies were detected by a semi-automated ELISA.¹³

Neuronal surface antibodies were detected by scoring the serum IgG binding to live transfected human embryonic kidney 293 cells expressing the antigens,^{14,15} with sera diluted 1:20 for LGI1 and NMDA receptor and 1:100 for CASPR2 and GABAB receptor. All positive results were repeated and read by a second observer and the sera tested for lack of binding to an alternative antigen. Patients with neurologic syndromes were analyzed for binding to live unpermeabilized cultured cerebellar granule cell neurons using a standard protocol and 1:200 serum dilution.¹⁶ For this, HC serum was used as a negative control and CASPR2-positive serum as a positive control.

Statistics. Two-sided (2-tailed) Fisher exact test p values were computed from contingency tables by the “method of summing small p values.” Median survival times were extrapolated from Kaplan-Meier plots using SPSS Version 17.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS Seventy percent of all Trent region patients with a new diagnosis of SCLC consented to the study ($n = 264$, median age 65 years, table 1). PNDs were identified by clinical evaluation in a total of 24 patients (9.1%). Exactly half of the patients with PNDs (12/24) had not been under neurology follow-up prior to attending the lung oncology clinic and were primarily evaluated by our team in that clinic; 8 of the 12 patients had neurologic symptoms before the cancer diagnosis.

The most prevalent PND was LEMS, affecting 10 patients (3.8% of cohort); 2 patients had coexisting cerebellar ataxia. Sensory neuronopathy (SN) was diagnosed in 5 patients (1.9%) and limbic encephalitis (LE) in 4 patients (1.7%). Other PNDs were found at low frequencies: paraneoplastic encephalomyelitis (PEM, 2 patients), dermatomyositis (2 patients), and paraneoplastic cerebellar degeneration (PCD, 1 patient). The neurologic symptoms preceded the cancer diagnosis in 20 patients (83%, range 1–13 months, table e-1 on the *Neurology*[®] Web site at Neurology.org).

Table 1 Epidemiologic data for small cell lung carcinoma and healthy control cohorts

	No. of individuals	Median age at recruitment, y	% with limited stage SCLC	Median survival, mo, Kaplan-Meier	% smoking for ≥ 15 pack-years ^a	% men
SCLC patients						
Whole cohort	264	65.0	39	9.8 (95% CI 8.9–10.6)	93	52
SCLC, PND	24	62.5	63	11.5 (95% CI 6.4–16.6)	92	54
SCLC, non-PND	240	66.0	36	9.5 (95% CI 8.8–10.2)	93	51
Healthy controls						
Whole cohort	38	68.0	NA	NA	34	71

Abbreviations: CI = confidence interval; NA = not applicable; PND = paraneoplastic neurologic disorder; SCLC = small cell lung carcinoma.

^aOne pack-year defined as the equivalent of 20 manufactured cigarettes (1 pack) smoked per day for 1 year, i.e., 7,300 cigarettes.

SOX2 antibodies were detectable in 15 (62.5%) patients with PNDs, a higher proportion than in SCLC patients without PNDs (23.8%, $p \leq 0.001$, table 2). Of the 15 PND patients with SOX2 antibodies, 9 had LEMS, 3 had SN, and 3 had LE.

Similarly, HuD antibodies were detectable in a higher proportion of patients with PND (41.7%) than patients without PND (9.6%) ($p < 0.001$). Four patients had SN, 2 LEMS, 2 PEM, 1 PCD, and 1 LE.

VGCC antibodies, especially P/Q subtype, were found in all 10 patients with LEMS and in 1 patient each with SN and LE.

Overall, 21/24 (87.5%) patients with PNDs were positive for antibodies to SOX2, VGCC, or HuD. The exceptions were 2 patients with dermatomyositis (1 Yo-positive, 1 negative on all assays) and 1 patient with LE (negative on all assays).

There was a lower frequency of neuronal antibodies in SCLC patients without detectable PNDs

(23.8% SOX2, 0.4%–9.6% all others, table 3). Only VGKC ($n = 3$ [7.9%], mean titer 240 pM) and NMDA receptor antibodies ($n = 1$ [2.6%], 1:640) were found in HCs. Of the 4 antibody-positive HCs, 1 (VGKC complex-positive) was a smoker.

Three of 24 patients with PNDs (2 LEMS, 1 LE) who had GABA_B receptor and P/Q-type VGCC antibodies showed antibody binding to live cerebellar neurons (figure e-1). Other patient sera with high levels of VGCC antibodies did not bind detectably to these neurons.

Improved survival was noted in patients with PNDs (median 11.5 months vs 9.5 months in SCLC patients without PNDs), but this did not reach statistical significance (log rank $p = 0.095$, figure e-2).

DISCUSSION In this single-region prospective study, we determined the frequency and spectrum of PNDs in 264 consecutive patients with SCLC

Table 2 Prevalence of neuronal antibodies

Neuronal antigen	Antibody prevalence in SCLC patients with PND (n = 24), n (%)	Associated PND (whole cohort = 10 LEMS, 5 SN, 4 LE, 2 PEM, 2 DM, 1 PCD)	Antibody prevalence in SCLC patients without PND (n = 240), n (%)	Antibody prevalence in healthy controls (n = 38), n (%)	p Value, Fisher exact test
Intracellular antigens					
SOX2	15 (62.5)	9 LEMS, 3 SN, 3 LE	57 (23.8)	0	0.001 ^{a,b,c}
HuD	10 (41.7)	2 LEMS, 4 SN, 1 LE, 2 PEM, 1 PCD	23 (9.6)	0	<0.001 ^{a,b}
GAD65	1 (4.2)	1 PEM	5 (2.1)	0	NS
Amphiphysin	0 (0)	0	6 (2.1)	0	NS
Ri	0 (0)	0	3 (1.3)	0	NS
CRMP5	1 (4.2)	1 SN	2 (0.8)	0	NS
Ma2	0 (0)	0	2 (0.8)	0	NS
Yo	1 (4.2)	1 DM	1 (0.4)	0	NS
Cell surface antigens					
VGCC (P/Q)	12 (50.0)	10 LEMS, 1 SN, 1 LE	10 (4.2)	0	<0.001 ^{a,b}
VGCC (N)	5 (20.8)	4 LEMS, 1 LE	6 (2.1)	0	<0.007 ^{a,b}
GABA _B receptor	3 (12.5)	2 LEMS, 1 LE	7 (2.9)	0	NS
VGKC complex	1 (4.2)	1 LEMS	15 (6.3)	3 (8)	NS
CASPR2	1 (4.2)	1 LEMS	1 (0.4)	0	NS
LGI1	0 (0)	0	0 (0)	0	NS
NMDA receptor	1 (4.2)	1 SN	1 (0.4)	1 (2.6)	NS
SOX2/HuD/VGCC (P/Q)	21 (87.5) positive for at least 1 of these antibodies	All except 2 DM and 1 LE	69 (28.8) positive for at least 1 of these antibodies	0	<0.001 ^a
All antibodies	22 (91.7) positive for ≥1 antibody	All except 1 DM and 1 LE	104 (43.3) positive for ≥1 antibody	4 (10.5) positive for ≥1 antibody	<0.001 ^a

Abbreviations: DM = dermatomyositis; LE = limbic encephalitis; LEMS = Lambert-Eaton myasthenic syndrome; PCD = paraneoplastic cerebellar degeneration; PEM = paraneoplastic encephalomyelitis; PND = paraneoplastic neurologic disorder; SCLC = small cell lung carcinoma; SN = sensory neuronopathy; NS = not significant.

^aSignificance: PND vs non-PND SCLC.

^bSignificance: PND vs HC.

^cSignificance: non-PND SCLC vs HC.

Table 3 Antibody profile of SCLC patients with PNDs

Diagnosis	SOX2 ELISA (mean optical density)	P/Q-type VGCC (mean titer, pM)	HuD	N-type VGCC (mean titer, pM)	GABA _B receptor (mean CBA score)	CRMP5/Yo/ Ri/Ma2/ amphiphysin	GAD65 (mean titer, U/mL)	NMDA receptor (mean CBA score, titration)	VGKC complex (mean titer, pM)	CASPR2 (mean CBA score, titration)	LG11	Cultured cerebellar neuron IHC
LEMS (n = 10)	9 (1.44)	10 (535)	2	4 (203)	2 (4)	0	0	0	1 (281)	1 (3, 1:800)	0	2
LE (n = 4)	3 (0.97)	1 (139)	1	1 (146)	1 (4)	0	0	0	0	0	0	1
SN (n = 5)	3 (1.13)	1 (105)	4	0	0	1 (CRMP5)	1 (654)	1 (1, 1:320)	0	0	0	0
PEM (n = 2)	0	0	2	0	0	0	0	0	0	0	0	0
PCD (n = 1)	0	0	1	0	0	0	0	0	0	0	0	0
DM (n = 2)	0	0	0	0	0	1 (Yo)	0	0	0	0	0	0
PND SCLC (n = 24)	62.5% (1.38)	50.0% (466)	41.7%	20.8% (435)	12.5% (4)	8.3%	4.2% (654)	4.2% (1, 1:320)	4.2% (281)	4.2% (3, 1:800)	0%	12.5%
Non-PND SCLC (n = 240)	23.8% (1.47)	4.2% (134)	9.6%	2.1% (161)	2.9% (2)	5.8%	2.1% (882)	0.4% (1.5, 1:320)	6.3% (161)	0.4% (1, 1:400)	0%	Not tested
Healthy controls (n = 38)	0%	0%	0%	0%	0%	0%	0%	2.6% (3, 1:640)	7.9% (240)	0%	0%	Not tested

Abbreviations: CBA = cell-based assay; DM = dermatomyositis; IHC = immunohistochemistry; LE = limbic encephalitis; LEMS = Lambert-Eaton myasthenic syndrome; PCD = paraneoplastic cerebellar degeneration; PEM = paraneoplastic encephalomyelitis; PND = paraneoplastic neurologic disorder; SCLC = small cell lung carcinoma; SN = sensory neuronopathy.

CBAs were scored on a visual scale based on positive control comparators: 0 (no specific binding) to 4 (most intense specific binding). A score of 1 or above indicated that specific binding was visualized (positive result).

from an unbiased population with representative demographics (table 1). SCLC PNDs were surprisingly prevalent (24 patients, 9.1%). Our data suggest that PNDs may be underrecognized: 12/24 patients had not seen a neurologist prior to attending the lung oncology clinic even though 8 of them had reported neurologic symptoms in the months preceding the lung cancer diagnosis.

Previous studies have reported the frequency of SOX, Hu, and VGCC antibodies in SCLC LEMS (65% SOX, 30% Hu, 100% VGCC),¹⁷ SCLC PCD (49% SOX, 31% Hu, 44% VGCC),¹⁸ and noncancer disease controls (0% SOX, 0% Hu, 0% VGCC).^{17,19} We additionally found clustering of these antibodies in SCLC LE and SN. Overall, we found that 87.5% of all PNDs were associated with SOX2, HuD, or P/Q VGCC antibodies ($p < 0.001$ compared with both HCs and SCLC patients without PNDs). Therefore, screening for all 3 antibodies will capture the majority of SCLC PNDs in a patient presenting with a suspicious neurologic syndrome.

We report a low frequency of SOX2/HuD/P/Q VGCC antibodies in non-PND SCLC (28.8%); their presence should raise the possibility of SCLC irrespective of the clinical syndrome, but sensitivity is insufficient for any combination of them to be a useful tumor marker in the absence of neurologic symptoms.

Of the synaptic proteins (including GAD65, NMDA receptor, and CASPR2), only GABA_B receptor antibodies were found at a significantly higher

frequency in PND SCLC (12.5%) than in non-PND (2.9%). In keeping with a previous study,²⁰ we found that GABA_B receptor antibodies coexist with both N- and P/Q-type VGCC antibodies in LE (the previous study recruited large numbers of patients with LE and demonstrated that GABA_B receptor antibodies cosegregate with N-type VGCC more than P/Q-type in LE). In addition, we found that 20% of SCLC LEMS patients (a P/Q VGCC antibody-mediated disease) were GABA_B receptor antibody-positive. This suggests that the respective antigens (N- and P/Q-type VGCC and GABA_B) co-localize in SCLC, as previously reported for SOX/VGCC.²¹

Cerebellar neuron staining was not observed in any VGCC-positive patients (other than those with coexisting GABA_B antibodies), possibly because neuronal VGCC antigens are clustered in active zones at the terminal button and not at a level that is easily detected by immunostaining.²²

Currently almost half of all patients diagnosed with PNDs have associated SCLC,² so this study is relevant to the broad epidemiology of these neurologic disorders. We found a higher frequency of PNDs (9.1% of SCLC) than previous SCLC surveys, perhaps because of the single-center prospective design with neurology input and high recruitment among the SCLC population. The findings suggest that PNDs in patients with SCLC may be underdiagnosed due to misattribution of symptoms; recognition of the disorders and their

common antibody associations is important because the earlier the diagnosis is made, the better the oncologic and neurologic outcome.^{23,24}

AUTHOR CONTRIBUTIONS

Dr. Gozzard wrote the first draft of the manuscript, participated in the design of the study, collected data, analyzed and interpreted the data, performed statistical analysis of the data, and edited the manuscript. Dr. Woodhall designed assays for the study and collected data. Dr. Chapman designed assays for the study and collected data. Ms. Nibber designed assays for the study and collected data. Dr. Waters designed assays for the study and revised the manuscript. Prof. Vincent analyzed and interpreted the data and revised the manuscript. Dr. Lang designed assays for the study, collected data, analyzed and interpreted the data, and revised the manuscript. Dr. Maddison conceptualized and designed the study, collected data, analyzed and interpreted the data, and revised the manuscript.

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DISCLOSURE

P. Gozzard and M. Woodhall report no disclosures relevant to the manuscript. C. Chapman reports grants and receives personal fees from On-cimmune Ltd. A. Nibber reports no disclosures relevant to the manuscript. P. Waters holds a patent on the detection of antibodies to CASPR2 and LGI1, with royalties paid by EuroImmun AG. A. Vincent reports grants from NIHR, receives personal fees from Athena Diagnostics, and holds a patent for VGKC complex antibodies licensed to Euro-immun AG for which she received royalties. B. Lang holds a patent for the use of LGI1 in diagnosis, with royalties paid to Oxford University. P. Maddison reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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