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Paraneoplastic neurological autoimmunity and survival in small-cell lung cancer

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Abstract

The autoimmune disorder of Lambert–Eaton myasthenic syndrome (LEMS) associates with small cell lung carcinoma (SCLC) in 50–60% of cases. It has been postulated that patients who harbour paraneoplastic neurological syndromes such as LEMS have an improved tumour prognosis compared to other patients with the tumour but without neurological deficit. In this intermediate report of an ongoing prospective study, 100 consecutive patients with biopsy-proven SCLC underwent full neurological examination and serum was taken for autoantibody analysis. Antibodies to voltage-gated calcium channels were detected in 10 patients, however only 4 had clinical and electrophysiological features of LEMS, 1 had limbic encephalitis, whilst the remaining 5 had no neurological signs. A further 6 patients had onconeural antibodies; only one had a paraneoplastic syndrome, sensory neuropathy. The median survival of the four antibody positive LEMS patients (19.6 months) was considerably greater than that for the antibody negative (8.9 months) or antibody positive patients as a whole (10.5 months). Although preliminary, these results suggest that functionally effective antibodies present in the sera of patients with LEMS may confer a survival advantage.

Keywords: Small-cell lung cancer; Lambert–Eaton myasthenic syndrome; Voltage-gated calcium channels; Onconeural antibodies; Survival

1. Introduction

A proportion of paraneoplastic neurological syndromes are thought to be immune-mediated, characterised by the detection of antibodies against neural antigens expressed by the tumour (for review, see Darnell and Posner, 2006). It is not clear whether well-characterised onconeural antibodies have a pathogenic functional effect: there are no directly-induced animal models following passive transfer of the patient sera; and certainly patients with typical anti-Hu, Yo or Ri antibodies do not usually respond effectively to immunomodulatory treatment. Therefore the pathogenic consequences from these paraneoplastic immune responses may be mediated through antigen-specific T-cell responses and the antibodies may simply be markers of this underlying immune response. However, the Lambert–Eaton myasthenic syndrome (LEMS), which associates with small cell lung carcinoma (SCLC) in approximately 50–60% of cases, may have a different aetiology as autoantibodies directed against cell-surface ion channels (e.g. voltage-gated calcium channel (VGCC) antibodies in paraneoplastic LEMS) seem to have a

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[1] It is through the unstinting support I received from John Newsom-Davis whilst working as the myasthenia research fellow in Oxford 10 years ago that led to the original finding of improved survival in patients with small-cell lung cancer who also developed Lambert–Eaton myasthenic syndrome (LEMS). He was always extremely keen that I continued to work on LEMS after leaving Oxford, resulting in several ongoing collaborative papers and reviews. Through regular contact since this time, he encouraged me to set up the current prospective paraneoplastic study, and it is only through JN-D's guidance and characteristically supportive and thorough appraisal that the current LEMS work has continued.

[2] Although the original report of a patient with LEMS was made by Anderson and his coworkers in 1953, it was Lambert, Eaton and Rooke in 1966 who described the clinical and electrophysiological findings of the disease that bear their name. Many features of LEMS suggested that it was an autoimmune disorder similar to myasthenia gravis; however it took a series of papers from John Newsom-Davis' group in the 1980s to finally establish the autoimmune aetiology of the disorder and define the antigenic target, the voltage-gated calcium channel. I was extremely privileged to be part of the group at that exciting time and owe so much to JND and Angela Vincent. So much of my scientific life has been guided by JND, who constantly suggested new and exciting avenues for my scientific research and who was so generous with his time in explaining clinical neurology to a basic scientist.

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functionally pathogenic role (Pinto et al., 1998, 2002; Lang et al., 1987).

What seems to be unresolved at present is whether the 'immune surveillance' seen in these well-defined immune-mediated paraneoplastic neurological syndromes improves tumour prognosis, compared with patients harbouring identical cancers but without an associated paraneoplastic neurological syndrome. It has been postulated that HLA class I-restricted cytotoxic T-lymphocyte tumour cell lysis may account for this possible beneficial effect (Morris et al., 1992; Albert et al., 1998). Nevertheless, most patients with paraneoplastic neurological syndromes such as SCLC-associated LEMS present with neurological symptoms before tumour diagnosis, offering the clinician a lead-time bias in terms of detecting an associated tumour at its earliest stage of development.

Previous survival studies have reported conflicting results. The presence of low-titre anti-Hu antibodies in a prospective study of 170 SCLC patients without paraneoplastic neurological symptoms was associated with tumours that were more often of limited dissemination at diagnosis, resulting in longer survival (Graus et al., 1997). In contrast, a study of 200 patients with SCLC revealed that low titres of anti-Hu antibody in 51 (26%) did not correlate with disease extent or survival (Monstad et al., 2004)., whilst a retrospective study of 57 SCLC patients with paraneoplastic cerebellar degeneration showed that the presence of anti-Hu antibodies was associated with a worse survival than antibody-negative patients, although most deaths were attributable to neurological deterioration (Mason et al., 1997).

More encouragingly, a prospective study of 148 SCLC patients revealed that patients with clinical symptoms and signs of LEMS and positive VGCC antibodies had improved survival but patients who were asymptomatic, or had another paraneoplastic neurological syndrome such as cerebellar degeneration had survival rates comparable to patients with SCLC alone (Wirtz et al., 2005). These findings were not reproduced in the study of Monstad et al., 2004 who showed that the presence of VGCC antibodies (10 patients, 5%) did not correlate with improved survival in a univariate analysis. However, it should be noted that these patients were not examined for the presence or absence of neurological signs of paraneoplastic neurological syndromes, including LEMS. The presence of clinical signs of LEMS in 15 patients with SCLC in a further retrospective study was associated with an improved survival compared with SCLC patients without LEMS, although the LEMS patient data were matched with historical controls (Maddison et al., 1999).

In this current prospective study of SCLC patients, we aimed to establish whether it is the presence of a clinically detectable neurological syndrome (such as LEMS) in patients with SCLC that confers a survival advantage and attempt to determine if this is due to the detection of the tumour at an earlier stage, or whether tumour immune surveillance, with detectable onconeural antibodies influences tumour prognosis, perhaps through a direct functional effect.

2. Materials and methods

2.1. Small-cell lung cancer patients

One hundred consecutive, unselected patients with biopsy-proven SCLC were recruited at time of tumour diagnosis from hospitals within the Trent region of the UK. These are the first 100 patients of an ongoing, large, prospective study of paraneoplastic neurological disorders in patients with SCLC (Nottingham Research Ethics Committee approval 04/Q2404/100). All patients underwent full neurological evaluation and examination, and serum samples were taken prior to chemotherapy, and stored at −80 °C for further analysis. Additional patients with characteristic paraneoplastic neurological syndromes were included in the study if further follow-up investigations revealed SCLC. Any patient initially included in the study who subsequently developed new neurological symptoms was seen again for review.

2.2. Paraneoplastic neurological syndrome diagnostic criteria

Patients were diagnosed as having LEMS if they showed typical clinical features of initial proximal, fatiguable lower limb weakness, autonomic dysfunction (dry mouth, blurred vision, erectile dysfunction), attenuated or absent tendon reflexes with or without reflex potentiation following 10 s maximal voluntary contraction, and lack of significant sensory abnormalities (O'Neill et al., 1988). Electromyography-supportive features were reduction in the resting compound muscle action potential amplitude (of abductor digiti minimi) with incremental responses of at least 60% following maximal voluntary contraction, or high rate repetitive nerve stimulation (Oh et al., 2005). Other paraneoplastic neurological syndromes, such as sensory neuronopathy, or paraneoplastic cerebellar degeneration, were diagnosed according to previously published clinical diagnostic criteria (Graus et al., 2004).

2.3. Antibody analysis

Autoantibodies in serum from patients with SCLC or controls were measured by immunoprecipitation of VGCCs extracted from human cerebellum and labelled with either ^{125}I-ω-CmTx MVIIC (P-/Q-type VGCC) or ^{125}I-ω-CgTx GVIA (N-type VGCC) as previously described (Motomura et al., 1997). Antibodies were considered positive if greater than 50 pM.

Antibodies to onconeuroantigens HuD, Yo, Ri, CV2 (CRMP5), amphiphysin and Ma2 were detected using an commercial immunoblot kit (RAVO Diagnostika. GmbH, Freiburg, Germany).

2.4. Statistical analysis

Student's *t*-test was used to compare means of datasets that approximated to a Gaussian distribution, verified by the Kolmogorov–Smirnov test. The difference in survival rates between patients with paraneoplastic neurological syndromes or positive onconeural antibodies and SCLC, and patients with SCLC alone were compared using log rank tests from Kaplan–Meier curves.

3. Results

3.1. Characteristics of antibody-positive patients

Overall, 10 patients (10%) had positive VGCC antibodies. Eight patients had P-/Q-type VGCC antibodies (range 70–