

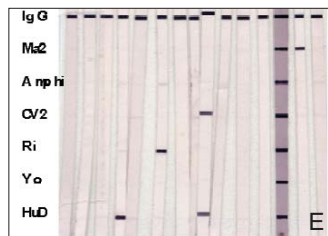
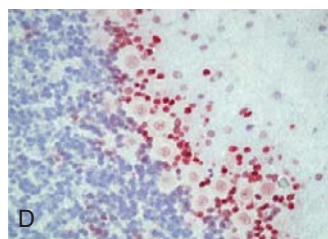
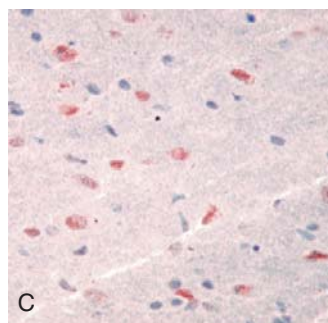
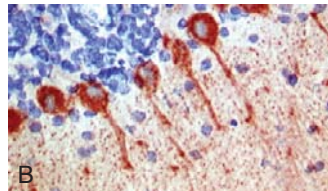
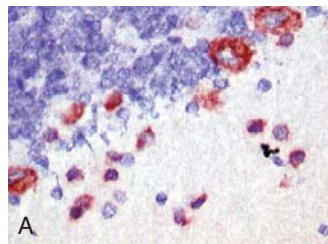
Paraneoplastic Neurological Diseases

Paraneoplastic neurological syndromes (PNS) are neurological disorders which are the indirect effect of a tumour, ie. in which there is no direct involvement of the tumour or its metastases or its treatment. Although some conditions can be caused by, for instance, alterations in the levels of circulating hormones or growth factors, the PNS are now generally thought of as immune-mediated conditions.

There are a number of classical syndromes in which a suspicion of PNS must always be considered (Table 1). The finding of an onconeural (paraneoplastic) antibody defines the neurological disease as being tumour-related and a search for the most likely tumour should be initiated. The PNS are not common diseases, affecting at most 5% of those with small cell lung cancer (SCLC) which is the most common PNS-associated tumour. In a recent survey conducted among UK physicians, around 50 PNS were reported in one year¹ which would give an approximate incidence of 1/million. However, there is likely to be under-recognition and under-reporting of these syndromes when the patients' symptoms may be inappropriately ascribed to tumour-associated morbidity or treatment effects. Criteria for classification of PNS as definite or possible have recently been proposed.²

The syndromes

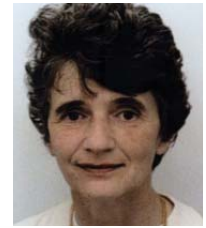
There are a number of classical PNS (Table 1). These can be rigorously defined by following clinical, MRI and other criteria which are summarised in several reviews.²⁻⁴ The typical PNS presents subacutely with progression over a period of around three months, after which it may stabilise or (if the patient survives) may take a progressive course.⁵ The clinical status can be assessed by a Rankin score.



Onconeural antibodies

The antibodies (Tables 1 and 2) were originally described by indirect immunohistochemistry on human or rodent brain sections (fixed in paraformaldehyde or acetone) by virtue of their very distinct patterns (e.g. Figure 1A-D). However, not all sera producing these patterns are specific for the paraneoplastic antigens and immunoblotting has to be performed to confirm the identity of any antibody. Fortunately, there are now commercial immunoblots which contain six characterised antigens so that serum testing can be performed in a more standardised manner (Figure 1E). Nevertheless, certain antigens (e.g. Tr, Figure 1B) are not available on the commercial immunoblots.

It is thought that the typical antineuronal antibodies, Hu, Yo, Ri, amphiphysin, CV2, Ma2 and Tr are extremely rare in patients without tumours, but it is possible that in some cases the tumour is occult throughout the life of the patient. On the other hand, some of the ion channel antibodies that can be associated with PNS are also found in non-paraneoplastic forms of the disorders (e.g. in Lambert Eaton myasthenic syndrome (LEMS), acquired neuromyotonia).⁶ The presence of Hu, CV2, or the recently described anti-glial nuclear antibody



Angela Vincent is Professor of Neuroimmunology at the University of Oxford and an honorary consultant in Immunology at the Oxford Radcliffe Trust. She heads the Neurosciences Group in the Weatherall Institute of Molecular Medicine, researching into antibody-mediated neurological diseases, and since 2005 has been Head of Department of Clinical Neurology.



Christian G Bien, MD, is a Senior Neurologist and Leading Assistant Medical Director at the Department of Epileptology at the University of Bonn, Germany. He is especially responsible for the presurgical assessment of pharmacoresistant epilepsy patients and has a special interest in immunologically mediated epilepsies.

Correspondence to:

Professor Angela Vincent,
MBBS MSc FRCPATH FMedSci,
Neurosciences Group,
Weatherall Institute of Molecular
Medicine,
John Radcliffe Hospital,
Oxford OX3 9DS.
Tel. 01865 222321
Fax. 01865 222402

Figure 1: Examples of immunohistochemical detection of onconeural antibodies binding to (A) Yo in the Purkinje cells, (B) Tr in the Purkinje cells and molecular layer (C) Ma/Ma2 in the brain stem, and (D) nuclei in the Bergmann glia. (E) Examples of immunoblots showing strong bands representing binding of different sera to (reading from left) HuD, Ri, HuD and CV2, and Ma2. Positives represent a mixture of different sera. Courtesy of Dr E Amyes and Mr James Hoy.

Table 1

Classical paraneoplastic syndromes	Well-recognised onconeural antibodies	Most common tumours
<i>Panencephalomyelitis</i>	<i>Hu, CV2, amphiphysin</i>	<i>SCLC, NSCLC, breast, thymoma</i>
<i>Subacute cerebellar degeneration</i>	<i>Yo, Hu, Tr, CV2, Amphiphysin, Ma</i>	<i>Ovary, breast, SCLC, NSCLC</i>
<i>Limbic encephalitis</i>	<i>Hu, Ma2, CV2, amphiphysin, hippocampal neuropil, VGKC</i>	<i>SCLC, NSCLC, testicular non-seminoma, testicular seminoma, thymoma, ovary, breast, prostate</i>
<i>Subacute sensory neuropathy</i>	<i>Hu, CV2, amphiphysin, Ma2</i>	<i>SCLC, NSCLC, prostate</i>
<i>Lambert Eaton myasthenic syndrome</i>	<i>VGCC, also Hu, amphiphysin, Yo, Ri, CV2, Tr</i>	<i>SCLC, NSCLC</i>
<i>Dermatomyositis</i>	<i>None</i>	<i>SCLC, NSCLC, ovary, breast, prostate</i>
<i>Opsoclonus myoclonus</i>	<i>Hu, Ri</i>	<i>SCLC, NSCLC, breast</i>
<i>Chronic gastro-intestinal pseudoobstruction</i>	<i>Hu, CV2</i>	<i>SCLC, NSCLC, breast</i>

Classical syndromes according to Graus et al (2004). Others that are 'non-classical' but which may be paraneoplastic include brainstem encephalitis, optic neuritis, cancer-associated retinopathy, stiff person syndrome, necrotising myelopathy, motor neuron disease, Guillain-Barré-Syndrome, brachial neuritis, other neuropathies, myasthenia gravis, acquired neuromyotonia. The antibodies listed, apart from Tr, are principally those that are widely available and well characterised, and available on immunoblots (e.g. Figure 1). Tr is not yet defined at the molecular level. VGCC and VGKC antibodies are also present in non-paraneoplastic cases and not available as part of any paraneoplastic screen, in the UK. They should be requested separately if appropriate. SCLC = Small cell lung cancer and NSCLC = non-small cell lung cancer.

(AGNA^{7,8}, see Figure 1D), should help to indicate an associated SCLC even in these cases.

Because the immune response is made in the periphery against the tumour, the antibodies are found at highest levels in the serum rather than in the CSF. The only exception may be the neuropil antibodies which are said to be easier to detect in the CSF.⁹ The reason for this is not clear.

The tumours

The tumours that are most frequently associated with PNS (Tables 1 and 2) are those with neuroendocrine origins, such as SCLC, or concerned with the immune system, such as thymomas and lymphomas. Non-small cell lung cancers (NSCLC) are also quite commonly associated with PNS. Tumours of ovary and breast and many others may also induce PNS.

There are two PNS that are worth highlighting. Young men (<50 years) presenting with limbic encephalitis, often with additional brainstem and hypothalamic symptoms, may have a testicular tumour, and detection of Ma2 antibodies is critical in pointing to this association.¹⁰ These patients appear to do reasonably well with treatment of the tumour and immunosuppression for the neurological syndrome. Young women (below 45 years, so far) with a limbic encephalitis and often a more global encephalopathy with severe disturbance of cognitive function, often central hypoventilation and dyskinesias, may have an ovarian or other teratoma associated with antibodies to 'neuropil' of the hippocampus, in some cases defined as NMDA receptors.⁹ These patients also are reported to do well with the appropriate treatments for the tumours and immunosuppression for the neurological syndrome.

Mechanisms

In most cases the antibodies are markers for the immune response directed against the tumour and are not in themselves pathogenic. This applies

particularly to the well characterised antibodies. The reasons for believing this is that the patients do not respond well to immunotherapies alone, and passive transfer of antibodies to experimental animals does not induce disease. Concordantly, the titre of Hu antibodies does not correlate with disease severity on longitudinal studies.¹¹ On the other hand, the pathology of the brain (Figure 2D) suggests that infiltrating T cells may be involved in producing inflammation and in directly attacking neurons. This is particularly likely to be the case in paraneoplastic cerebellar degeneration where loss of Purkinje cells has been demonstrated in post-mortem tissue. Although T cell studies have not

Case vignette:

A 50-year-old lady with a longstanding history of cigarette smoking presented with the following complaints: Starting three years ago, she had been experiencing attacks typical of simple partial temporal lobe seizures, a disturbance of recent memory, and weight loss. Standard blood and CSF laboratory values including microbiological search for common neurotropic viruses were unremarkable. Brain MRI revealed a temporomedial high intensity FLAIR signal clearly greater on the right side (Figure 2A). Testing for onconeural antibodies by indirect immunohistochemistry on rat brain revealed a pattern typical for AGNA (Figure 2B). A tumour search revealed a left hilar pulmonary mass (Figure 2C) which was found to represent a SCLC with limited disease. The diagnosis was paraneoplastic limbic encephalitis with SCLC associated with AGNA. Following surgical, chemotherapeutic and radiation therapy, the patient has been relapse free for a follow-up of 2.5 years up to now. The neurological syndrome has remained unchanged.

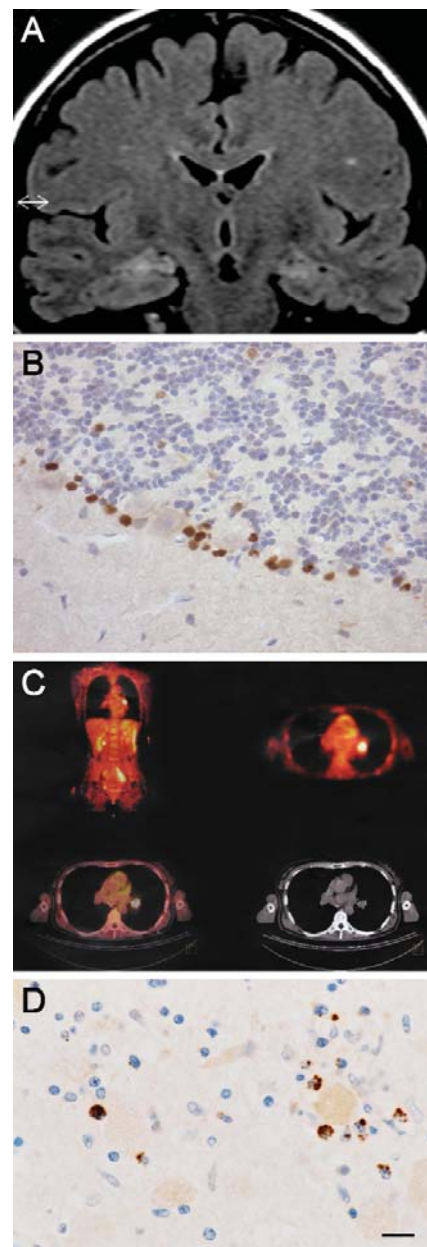


Figure 2: Case of a 50-year-old female patient with paraneoplastic limbic encephalitis with small cell lung cancer and serum antibodies against AGNA. (A) Coronal brain FLAIR MR image indicating increased hippocampal signal without atrophy. (B) [18F]-fluorodeoxyglucose positron emission tomography coregistered with CT reveals a left hilar hypermetabolic mass. Histological diagnosis: small cell lung cancer, limited disease (C) Indirect immunohistochemistry showing staining of patients serum on paraformaldehyde fixed rat brain. Note the nuclear staining of the Bergmann glia in the Purkinje cell layer of the cerebellum. (D) Brain stem section of a deceased patient with paraneoplastic encephalomyelitis associated with Ma2 antibodies and lung carcinoma, immunohistochemical staining for the cytotoxic protein granzyme B: Multiple granzyme B positive (i.e. cytotoxic) T lymphocytes attached to two neurons (bar:20µm).

Table 2: The onconeural antibodies and associated tumours

Table 2: The onconeural antibodies and associated tumours	
Well characterised antibodies	
<i>Hu</i>	<i>SCLC, other</i>
<i>Yo</i>	<i>Breast, gynaecological</i>
<i>Ri</i>	<i>Breast, gynaecological, SCLC</i>
<i>CV2</i>	<i>SCLC, thymoma, other</i>
<i>Amphiphysin</i>	<i>Breast, SCLC</i>
<i>Ma2/Ta</i>	<i>Testicular or other solid tumours</i>
<i>Tr*</i>	<i>Hodgkins lymphoma</i>
Not widely recognised yet but can be helpful	
<i>Zic4, ANNA3, PCA2, Sox1</i>	<i>SCLC</i>
<i>Hippocampal neuropil including NMDAR</i>	<i>Teratoma of the ovary</i>
<i>Retinal antigens eg. recoverin</i>	<i>SCLC or melanoma</i>
Antibodies associated with treatable syndromes	
<i>Ma2 antibodies, usually young males</i>	<i>Germ cell tumours of testis</i>
<i>Neuropil antibodies including NMDAR</i>	<i>Teratomas (ovarian)</i>
<i>Ganglionic AChR, autonomic neuropathies</i>	<i>SCLC, others</i>
<i>VGCC, LEMS</i>	<i>SCLC</i>
<i>VGKC, neuromyotonia, limbic encephalitis</i>	<i>Thymoma, others</i>
<i>AChR, myasthenia gravis</i>	<i>Thymoma</i>
*Tr is not a well characterised antibody but can be readily recognised by its distinctive staining pattern on cerebellum. SCLC = small cell lung cancer	

Table 3: Some points to remember

Look for subacute onset, expanding MRI lesions, early progressive course often with stabilisation after a few months

There may be more than one clinical syndrome

Tumour may not be found for up to five years (or even more sometimes)

Specific onconeural antibodies are not present in all cases

The tumour may be atypical

There may be more than one tumour

Detection of a well characterized onconeural antibody justifies a whole body CT-PET scan.

been extensive, they have shown some evidence of antigen specific T cells which could be directly pathogenic (reviewed in reference 12).

These concepts do not, however, apply to PNS with ion channel antibodies. In myasthenia gravis, Lambert Eaton myasthenic syndrome and acquired neuromyotonia, the diseases do respond well to immunotherapies even in those with aggressive SCLC or malignant thymoma. This is also the case with autonomic neuropathies associated with ganglionic AChR antibodies,¹³ and is likely to be the case with newly defined limbic encephalitis syndromes which are associated with VGKC antibodies (see reference 6). This condition is usually non-paraneoplastic but can be associated with thymomas or other tumours. In both cases the response to immunotherapy is very good, with substantial clinical improvement.

Treatment

The primary therapeutic efforts in cases of PNS should be directed against the underlying neoplasm, but immunological treatments should also be tried. Successful tumour treatment is associated with a halt in neurological disease progression in about two-thirds of the patients.¹⁴ Even in the absence of a large body of data (let alone high-grade trial evidence), some experience with immunotherapy directed against the immune reaction in the nervous system is available: In LEMS and myasthenia gravis, intravenous immunoglobulins and plasma exchange are effective therapeutic options for suppressing the immune response.¹⁵ In paraneoplastic encephalomyelitis including cerebellar degeneration, on the other hand, immunosuppressive or immunomodulatory therapies have in

general been rather disappointing with a majority of patients having progressive neurological disease.¹⁶ Ma2 antibody associated PNS seems to be an exception to the rule because about half of the patients stabilise or even improve on therapy.¹⁰ Fortunately, immunotherapy does not seem to be associated with a more rapid tumour progression. Therefore, immunotherapy (immunoglobulins, methylprednisolone, cyclophosphamide or a combination of those) from early on in conjunction with tumour treatment is recommended^{11,17} especially if the patient's neurological condition deteriorates rapidly. In cases of disease progression despite treatment, escalation of immunotherapy with increasing risks of side effects should be used with caution. Usually, patients deteriorate or are left with significant disability despite immunosuppressive or immunomodulatory treatment.

Conclusions

Detection of a specific antibody and recognition of a condition as paraneoplastic is important because the information has aetiological and prognostic relevance, and treatment of an underlying tumour often stabilises disease progression. However, it should be appreciated that despite the very important guidelines and associations between different syndromes, antibodies and tumours, there are often exceptions to these rules. Table 3 highlights some points to remember.

References

1. Candler PM, Hart PE, Barnett M, Weil R, Rees JH. A follow up study of patients with paraneoplastic neurological disease in the United Kingdom. *J Neurol Neurosurg Psychiatry* 2004;75:1411-5.

- Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135-40.
- Bataller L, Dalmau JO. Paraneoplastic disorders of the central nervous system: update on diagnostic criteria and treatment. *Semin Neurol* 2004;24(4):461-71.
- Bien CG, Elger CE. Limbic encephalitis: A cause of temporal lobe epilepsy with onset in adult life. *Epilepsy Behav.* 2007;10:529-38.
- Poepel A, Jarius S, Heukamp LC, Urbach H, Elger CE, Bien CG, Voltz R. Neurological course of long-term surviving patients with SCLC and anti-Hu syndrome. *J Neurol Sci* in press 2007.
- Buckley C, Vincent A. Autoimmune channelopathies. *Nat Clin Pract Neurol.* 2005;1:22-33. Review.
- Graus F, Vincent A, Pozo-Rosich P, et al. Anti-gliol nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. *J Neuroimmunol* 2005;165:166-71.
- Zuliani L, Saiz A, Tavolato B, Giometto B, Vincent A, Graus F. Paraneoplastic limbic encephalitis associated with potassium channel antibodies: value of anti-gliol nuclear antibodies in identifying the tumour. *J Neurol Neurosurg Psychiatry* 2007;78:204-5.52.
- Dalmau J, et al. 2007. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol.* 61: 25-36.
- Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, Saiz A, Meneses P, Rosenfeld MR. *Clinical analysis of anti-Ma2-associated encephalitis.* *Brain* 2004;127:1831-44.
- Llado A, Mannucci P, Carpentier AF, Paris S, Blanco Y, Saiz A, Delattre JY, Graus F. Value of Hu antibody determinations in the follow-up of paraneoplastic neurological syndromes. *Neurology* 2004;63:1947-9.
- Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N.Engl.J Med.* 2003;349:1543-54.
- Vernino S, Adamski J, Kryzer TJ, Fealey RD, Lennon VA. Neuronal nicotinic ACh receptor antibody in subacute autonomic neuropathy and cancer-related syndromes. *Neurology.* 1998;50:1806-13.
- Keime-Guibert F, Graus F, Broet P, Rene R, Molinuevo JL, Ascaso C, Delattre JY. Clinical outcome of patients with anti-Hu-associated encephalomyelitis after treatment of the tumor. *Neurology* 1999;53:1719-23.
- Bain PG, Motomura M, Newsom-Davis J, Misbah SA, Chapel HM, Lee ML, Vincent A, Lang B. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. *Neurology* 1996;47:678-83.
- Keime-Guibert F, Graus F, Fleury A, Rene R, Honnorat J, Broet P, Delattre JY. Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (Anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. *J Neurol Neurosurg Psychiatry* 2000;68:479-82.
- Vedeler CA et al. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. *Eur J Neurol.* 2006;13: 682-90.

INTERNATIONAL NEUROIMMUNOLOGY SYMPOSIUM

13th and 14th March, 2008
DUBLIN, IRELAND
Conway Institute, University College Dublin

Plenary lectures and oral presentations will cover:

Neurobiology and immunology; Cytokines and chemokines; Innate immunity - Immunoregulatory mechanisms; Immunology in neurodegenerative diseases; Glial cell function; Neurobiology of autoimmune diseases; TLR signalling and NF- κ B pathway in neuroinflammatory conditions; Neuroimmunology of viral infections in the CNS; Neuro-immuno-endocrine network

Abstract Submission: Abstracts are invited which cover basic science and clinically relevant aspects of neuroimmunology
Deadline for abstract submission: **15th November, 2007.**

www.ucd.ie/mniest/mniest_index.html



Under the auspices of the
European Union 6th
Framework Programme

