A paraneoplastic neurological disorder (PND) may be defined as one in which a particular neoplasm associates with a remote but specific effect on the nervous system more frequently than would be expected by chance. The range of tumours that can provoke these disorders is relatively limited. The commonest is small cell lung tumour, where a prospective study of 150 cases detected a paraneoplastic disorder in about 3%. This would imply that about 250 new cases a year in the UK are associated with this neoplasm, but in practice it seems that the diagnosis is often overlooked. Other neoplasms commonly implicated in PND are ovarian and breast cancers, neuroblastoma, thymoma and lymphoma. Diagnosis is often hampered by the fact that in most cases the onset of the neurological syndrome precedes the cancer declaring itself, sometimes for as long as five years.

Clinical syndromes

The range of syndromes is restricted, like the tumours that can cause them (Table 1), and encompasses the central (CNS) and peripheral nervous systems. The CNS syndromes are typically subacute in onset. More than one syndrome may be present in the same patient.4

Paraneoplastic encephalomyelitis (PEM) in its limbic form is characterised by confusion, memory loss and hallucinations. When the brain stem is involved, there may be pareses, deafness, diplopia, vertigo and central respiratory failure. There can also be involvement of the autonomic system. Magnetic resonance brain imaging may show areas of abnormal signal, and the pathological changes are those of multifocal inflammatory infiltrates. Patients with paraneoplastic cerebellar degeneration (PCD) experience trunk and limb ataxia, vertigo, nausea and sometimes diplopia. Imaging may reveal cerebellar atrophy, and at autopsy there is a striking loss of cerebellar Purkinje cells.

Opsoclonus-myoclonus (O-M) describes patients with oscillopsia (chaotic eye movements), vertigo, ataxia and limb myoclonus.

Paraneoplastic sensory neuropathy (PSN) is typically painful and sometimes asymmetrical. Pathologically, it is a dorsal root ganglionopathy characterised by inflammatory cell infiltrates and loss of neurons.

A less well-known syndrome, paraneoplastic neuromyotonia (NMT), can also occur in a non-paraneoplastic form. It is characterised by myokymia (spontaneous muscle twitching), sometimes with muscle hypertrophy, cramps, increased sweating and occasionally CNS changes (hallucinations, mood change). Creatine kinase may be raised.

In the Lambert-Eaton myasthenic syndrome (LEMS), the best characterised of these syndromes, only 60% of cases are paraneoplastic. It comprises proximal muscle weakness that is fatiguable, and first affects walking, loss of tendon reflexes that show post-tetanic potentiation, and autonomic dysfunction (dry mouth, constipation and erectile failure). Freeze-fracture electron microscopy reveals loss of presynaptic active zone particles that represent voltage-gated calcium channels (VGCC), and which is responsible for the reduced quantal release of transmitter.

Myasthenia gravis (MG) is a paraneoplastic disorder in the 10% of cases in which it is associated with thymoma. Its phenotype does not differ from non-neoplastic MG – that is, fatiguable muscle weakness that can affect ocular, limb, bulbar and respiratory muscles. The weakness results from the loss of functional muscle acetylcholine receptors (AChRs).

Neurological syndromes and their associated neoplasms and antibodies

The relationship between a neurological syndrome and its associated tumour is complex, in that a particular syndrome can occur with more than one tumour type and several different syndromes can associate with a particular neoplasm. For example, PCD can occur with gynaecological cancers (particularly ovarian), small cell lung cancer and Hodgkin’s lymphoma (when it appears

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Neoplasm</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalomyelitis</td>
<td>small cell lung, thymoma</td>
<td>anti-Hu, anti-CV2</td>
</tr>
<tr>
<td>Cerebellar degeneration</td>
<td>gynaecological, small cell lung, Hodgkin’s lymphoma</td>
<td>anti-Ho, anti-VGCC, anti-Tr</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus</td>
<td>neuroblastoma, breast</td>
<td>anti-Hu, anti-Ri</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>small cell lung, thymoma, small cell lung</td>
<td>anti-Hu, anti-VGKC</td>
</tr>
<tr>
<td>Lambert-Eaton</td>
<td>small cell lung, thymoma</td>
<td>anti-VGCC, anti-AChR</td>
</tr>
</tbody>
</table>

AChR = acetylcholine receptor; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel.
The principal central and peripheral neurological syndromes, their associated tumours and, for each tumour, its associated autoantibody are listed in Table 1. However, antibodies are not detectable in all patients with paraneoplastic neurological syndromes, so their absence does not exclude paraneoplastic disease.

As Table 1 illustrates, a single syndrome may have more than one associated serum autoantibody. The terminology used to describe some of these antibodies is based on the first two letters of the last name of the first person in whom the autoantibody was identified (eg anti-Hu, anti-Ri, anti-Yo). Some antibodies can be detected by immunohistology and/or by Western blotting (eg anti-Hu, anti-Ri, anti-Yo), while anti-ion channel antibodies can be detected by radioimmunoassay. The target specificities of these antibodies and the principal sites at which they are found are given in Table 2.

**Intracellular targets**

The targets have been identified in some cases as intraneuronal nuclear proteins (eg 35 kDa and 40 kDa proteins for anti-Hu antibodies, 55 kDa and 80 kDa proteins for anti-Ri), and in others they are primarily cytoplasmic (eg 34 kDa and 62 kDa proteins for anti-Yo). Further molecular characterisation of some of these intracellular targets has identified them as RNA-binding proteins. Amphiphysin, the antigenic target in some patients with PEM in association with breast cancer, is a synaptic protein of 128 kDa concerned with transmitter release.

**Transmembrane ion channels**

Intracellular targets need to be distinguished from those that are transmembrane ion channels: for example, the neuronal VGCC or voltage-gated potassium channels (VGKC), and the ligand-gated muscle AChRs. These ion channel targets each have extracellular domains. At the nerve-muscle junction, they lack the protection provided by the blood-brain barrier for CNS antigens.

**Antigenic stimulus**

There seems no doubt that the primary stimulus for the production of these antibodies is the expression of the relevant (onconeural) antigen by the tumour itself. In almost all cases, these antigens have been identified within the cytoplasm, nucleus or cell membrane of the tumour cell. Immune cell infiltration, particularly by macrophages, appears to be more prominent where there is an associated paraneoplastic syndrome.

**Effector mechanisms**

**Serum autoantibodies**

In considering the possible role of the many different serum autoantibodies identified in these syndromes, the criteria for categorising the associated disorder as autoimmune should be kept in mind. Demonstration of a humoral response to an onconeural antigen alone is not sufficient evidence. First, it needs to be shown that the disorder can be transferred to experimental animals by the patient’s serum or immunoglobulins (Ig); secondly, that immunisation with the affinity purified antigen reproduces the disorder, and that this can also be transferred by passive immunisation. Of the disorders considered here, only MG and possibly LEMS meet both these criteria. NMT has been successfully passively transferred from experimental animals to patients with PEM in association with breast cancer.

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**Table 2. Antibody target specificities.**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Target specificity</th>
<th>Principal sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalomyelitis</td>
<td>35–40 kDa protein (Hu) 66 kDa protein (CV2) amphiphysin</td>
<td>neuronal nuclei oligodendrocyte cytoplasm synaptic vesicle-associated</td>
</tr>
<tr>
<td>Cerebellar degeneration</td>
<td>34, 62 kDa proteins (Yo)</td>
<td>Purkinje cell cytoplasm</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus</td>
<td>55, 80 kDa proteins (Ri)</td>
<td>neuronal nuclei</td>
</tr>
<tr>
<td>Sensory neuropathies</td>
<td>35–40 kDa protein (Hu) VGKC</td>
<td>neuronal nuclei nerve-terminal membrane</td>
</tr>
<tr>
<td>Lambert-Eaton</td>
<td>VGCC</td>
<td>nerve-terminal membrane</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>AchR</td>
<td>muscle membrane</td>
</tr>
</tbody>
</table>

AChR = acetylcholine receptor; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel.

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© Commonest associated neoplasms are small cell lung cancer, gynaecological cancers, thymoma and neuroblastoma

© Serum antibodies are provoked by tumour antigens

© Antibodies to membrane ion channels are disease-inducing

© Antibodies to intracellular neuronal antigens are specific tumour markers

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Thus, tumour cell destruction might be expected to lead to release of intracellular antigens that are normally sequestered, followed by their ingestion by antigen-presenting cells such as dendritic cells, which could be responsible for stimulating the specific onconeural antigenic response. Furthermore, specific tumour therapy in LEMS can lead to recovery from the neurological syndrome, consistent with the view that tumour antigen plays a key role in provoking the humoral immune response.
to mice, and NMT IgG applied to rat dorsal root ganglion cells in culture causes repetitive firing consistent with the downregulation of VGKCs. Patients with these three disorders will usually show a response to plasma exchange. By contrast, attempts at passive transfer of the anti-Hu and anti-Yo syndromes have been unsuccessful, while active immunisation of experimental animals provokes a vigorous autoantibody response, but no disease. Patients with these syndromes do not respond to plasma exchange.

The data concerning the pathogenicity of the principal serum autoantibodies considered here are summarised in Table 3. The antigens in the anti-Hu and anti-Yo syndromes lack extracellular domains (also true, for example, for anti-Ri and amphiphysin) and would therefore not be accessible to circulating antibodies. Thus, despite their prominence, serum autoantibodies to onconeural antigens in many PNDs (eg O-M, PEM, PCD, PSN) are not the effector mechanism. One exception might be the group of anti-Hu negative PCD patients in whom anti-VGCC antibodies are detectable, since the latter can be present in the cerebrospinal fluid and can reduce calcium currents in cultured cerebellar Purkinje cells.

Cellular mechanisms

Cellular mechanisms seem likely to be implicated as the effector mechanism in those disorders which do not meet the criteria for an autoantibody-mediated disorder. The evidence is currently mainly circumstantial, but includes the pathological findings of multifocal cellular infiltrates, particularly in PEM, and the limited Vb repertoire of the receptors of the infiltrating T cells. In addition, (class I restricted cytotoxic T cells have been identified specific for the onconeural antigen in anti-Yo positive PCD patients, and which may have been sensitised by dendritic cells that have engulfed dying tumour cells.

Specific therapy and prognosis

The humorally-mediated disorders may respond to:

- plasma exchange,
- intravenous Ig,
- treatment of the tumour in LEMS, and
- immunosuppressive treatment with prednisolone in some cases.

By contrast, neither tumour treatment nor immunosuppression is effective in the other disorders.

Summary

Distinct syndromes are associated with a limited range of tumours. Autoantibodies are provoked by tumour (onconeural) antigens. Paraneoplastic antibodies to ion channels (VGCC, VGKC, AChR) are disease-inducing, but may also slow tumour growth in the case of LEMS. Antibodies to intracellular antigens in CNS disorders are probably not disease-inducing, but are valuable in diagnosis as disease markers. T cell mediated cytotoxicity is the likely effector mechanism in these latter disorders.

References


Table 3. Evidence of antibody pathogenicity.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Extracellular</th>
<th>Passive</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>AChR</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>VGCC</td>
<td>yes</td>
<td>yes</td>
<td>?</td>
</tr>
<tr>
<td>VGKC</td>
<td>yes</td>
<td>yes</td>
<td>not done</td>
</tr>
<tr>
<td>Hu</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Yo</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

AChR = acetylcholine receptor; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel.