What the general neurologist needs to know about paraneoplastic syndrome

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Figure 1 Small cell lung cancer reacting to 1:500 dilute serum from a patient with ANNA-1 antibody and sensory neuropathy. This shows positive immunoperoxidase staining of the tumour cells.

INTRODUCTION
The term paraneoplastic syndrome is now mainly reserved for non-metastatic manifestations of cancer that are considered to have some immunological explanation, i.e. they are not due to vascular disease, coagulopathy, infection, metabolic disorder, nutritional deficiency or the complications of treatment. The frequency of neurological paraneoplastic syndromes is something less than 0.5 per 100,000 population per year. Over the last 10 years, there has been increasing understanding of their immunological mechanisms and many new antigens/antibodies have been described. It is likely that the next few years will see the description of even more and so the number of ‘antibody negative’ cases will continue to shrink.

PATHOGENESIS
The central theory of pathogenesis is that the syndromes are autoimmune in origin. The individual patient mounts an antibody response to one or more of their tumour antigens, and the antibodies produced cross react with molecular domains normally expressed on neurones. (Fig. 1). This process then sets up an inflammatory response in the neural tissue. In most cases the actual immuno-pathogenic mechanism is uncertain because passive transfer of the antibodies to animals does not reproduce the clinical syndrome, or the pathology.
WHAT ARE THE COMMON CLINICAL PRESENTATIONS OF PARANEOPLASTIC SYNDROMES?

The clinical syndromes can be best categorized by the site of the neurological impairment (Table 1) and the type of serum antibody identified (see below).

Cerebral syndromes
Paraneoplastic encephalomyelitis (PEM) can affect any level of the CNS. Symptoms and signs precede the diagnosis of cancer by some months or years in more than 50% of cases. Patients are invariably adults who may present with subacute memory failure and cognitive problems, epileptic seizures, brain stem or cerebellar symptoms, or myelitis with spastic paraparesis (Dalmau et al. 1992; Graus et al. 2001). Commonly there is a mixture of neurological signs localizing to different levels in the CNS, often with downbeat nystagmus.

Paraneoplastic limbic encephalitis (PLE) is very uncommon and usually presents just with a subacute amnesic syndrome, often with a change in mood (Gultekin et al. 2000). Pathologically there is almost always extensive neuronal loss in the amygdala and hippocampus associated with microglial nodules (Fig. 2). There is short-term anterograde amnesia with variable retrograde amnesia, often associated with denial and confabulation (Alamowitch et al. 1997). The mood change may be depression or anxiety and can

Table 1 The paraneoplastic syndromes classified according to their main clinical manifestations

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<th>Cerebral</th>
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<td>Paraneoplastic limbic encephalitis (PLE)</td>
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<td>Eye</td>
<td>Paraneoplastic opsoclonus, myoclonus and ataxia (OMA)</td>
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<td>Peripheral nerves</td>
<td>Paraneoplastic sensory neuropathy (PSN)</td>
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<td>Neuromuscular junction</td>
<td>Paraneoplastic motor neuropathy (PMN)</td>
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Figure 2 H&E section of parahippocampal cortex demonstrating (a) microglial aggregates and (b) perivascular cuffing in a case of limbic encephalitis.
The central theory of Pathogenesis is that the syndromes are autoimmune in origin

be associated with personality change. Paranoia and hallucinations can occur. Late onset epilepsy around the time of diagnosis is quite common and helps distinguish this as being organic rather than a purely psychiatric condition. The seizures may be partial or generalized.

Although PEM and PLE can be isolated syndromes, they are often accompanied by other paraneoplastic neurological syndromes, especially sensory neuropathy or the Lambert-Eaton myasthenic syndrome.

Differential diagnosis includes any subacute CNS disturbance: space occupying lesions; intracranial venous thrombosis; viral or bacterial meningo-encephalitis; vasculitis and other inflammatory conditions; nutritional deficiency; metabolic/endocrine problems; toxic/drug related problems; direct effects of cancer (e.g. malignant meningitis); and psychiatric problems (psychosis, depression).

Cerebellar and brain stem syndromes

Paraneoplastic cerebellar degeneration (PCD) presents acutely over a few days or subacutely over some weeks. Patients develop a symmetrical or asymmetrical cerebellar syndrome affecting gait, speech and upper limbs associated with nystagmus (especially downbeat). Vertigo, nausea or vomiting may also occur (Anderson et al. 1988a). Patients are usually referred quickly because of the dramatic onset, severity and rapidly progressing disability.

Paraneoplastic opsoclonus, myoclonus and ataxia (OMA) occurs in adults as a paraneoplastic syndrome (Anderson et al. 1988b). Opsoclonus can be defined as involuntary, chaotic and repetitive rapid eye movements. Most adults who develop opsoclonus, myoclonus and ataxia are not known to have cancer at the time of presentation and it may be some months or years before a cancer diagnosis is made. Presentation is always dramatic and rapid. The eye movement disorder may be either true opsoclonus or ocular flutter. This is often associated with vertigo, vomiting and truncal ataxia of different degrees of severity. The myoclonus may be present at onset or may develop later. Respiratory and palatal myoclonus have also been described. OMA may be associated with other signs of paraneoplastic CNS involvement such as confusion, brain stem and corticospinal tract signs and the stiff man syndrome (Casado et al. 1994). Children who present with OMA usually have a neuroblastoma or a non-paraneoplastic cause (e.g. viral).

Differential diagnosis of PCD and OMA is that of any subacute central nervous system presentation affecting the cerebellum and brain stem and is broadly similar to PLE/PEM. In addition, listeria, viral labyrinthitis and cerebellitis (measles, chickenpox), alcohol, drugs and toxins (amitriptyline overdose, cytosine arabinoside, 5-fluorouracil, anticonvulsant toxicity and heavy metals) and olivopontine cerebellar atrophy need to be considered.

The eye

Paraneoplastic retinopathy (PR) is very rare. It can be associated with carcinoma and, as with the other paraneoplastic syndromes, it is the presenting complaint and precedes the discovery of the cancer by months to years. However, in melanoma-associated retinopathy the melanoma is known of at the time of presentation in virtually all cases. The degeneration of the retina affects the inner and outer segments of the cones and rods, and the outer nuclear layer. There is also a lymphocytic infiltration around the retinal arterioles. Patients present with asymmetrical painless blurring of vision that in time becomes bilateral and profound. Night blindness may be the only initial complaint. Photosensitivity, shimmering of vision and episodic obscurations of vision occur frequently. Symptoms progress over weeks or months to blindness. Examination shows visual impairment that includes colour vision in some cases and half of cases have afferent pupillary defects. Central vision is more commonly affected although ring scotomas, and constricted fields have also been reported.

Differential diagnosis is moderately straightforward when the cancer is known. However, infiltration of the optic nerve as part of malignant meningitis should be excluded. Toxic optic nerve and retinal damage from radiotherapy or chemotherapy, Leber’s optic neuropathy, vascular...
litis (giant cell arteritis) and multiple sclerosis also need to be considered.

**Peripheral nerves**

**Paraneoplastic sensory neuropathy (PSN)** is one cause of a pure sensory neuropathy in adults. The neurological syndrome almost always precedes the diagnosis of a tumour by some months or years. It presents with subacute numbness and paraesthesia, which can be asymmetrical and patchy initially, usually affecting the limbs although the trunk and face can also be involved. The neuropathy is often painful (shooting, burning pains). The large sensory fibres are frequently affected, giving a sensory ataxia and pseudoathetosis. Reflexes are almost always reduced or absent. The sensory neuropathy often occurs along with other paraneoplastic syndromes (generally anti-Hu related), for example limbic encephalitis, seizures, encephalomyelitis, autonomic disorder or cerebellar degeneration, which helps establish the neuropathy as being highly likely to be paraneoplastic. The condition progresses quite quickly over days or weeks to give severe disability, but this may stabilize. Slower presentations have been described.

**Paraneoplastic motor neuropathy (PMN)** can present like motor neurone disease or a demyelinating motor neuropathy and be clinically indistinguishable from these conditions. The picture is of acute or subacute weakness of the limbs associated with reduced or absent reflexes and without any significant sensory signs. There may be fasciculations in the muscles. The neurological syndrome almost always precedes the diagnosis of a tumour by some months or years, but may be the presenting feature in lymphoma. The features that alert to a paraneoplastic association are: the presence of other recognizable paraneoplastic syndromes or suspicious signs (e.g. PLE, PEM, downbeat nystagmus, etc.); a paraprotein in the blood; a bone lesion on skeletal survey (osteolytic or osteosclerotic myeloma); organomegaly and endocrinopathy as part of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy; M-protein; skin (hyperpigmentation/hyperhiderosis).

**Neuromuscular junction**

**Paraneoplastic Lambert–Eaton myasthenic syndrome (LEMS).** Fifty to sixty percent of patients with LEMS have an underlying tumour. Paraneoplastic LEMS precedes the diagnosis of cancer in the vast majority of patients, by up to 5 years. Small cell lung cancer is most common. The main differential is between myasthenia gravis and other causes of myopathy.

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**WHAT DIAGNOSTIC TESTS ARE THERE?**

**Paraneoplastic encephalomyelitis and limbic encephalitis** can be associated with a variety of serum (and CSF) antibodies (Moll et al. 1995). By far the most common is antineuronal nuclear antibody (ANNA-1 or anti-Hu) (Dalmau et al. 1990) (50% of patients) (Fig. 3). Thirty to forty
percent are antibody negative. Anti-Ma/Ta account for about 5% of cases and several other antibodies have been found in isolated cases or very small series (Rosenfeld et al. 2001). ANNA-1, ANNA-3, anti-CV2, PCA-2 and anti-tiamphiphysin are virtually always associated with small cell lung cancer (Antoine et al. 1999).

Anti-MA2 or anti-Ta are commonly associated with testicular germ cell tumours in males and occasionally lung and breast cancer in women. Anti-potassium channel antibodies or anti-CV2 can be found in patients with thymoma or lung cancer (Honnorat et al. 1996). False positive autoantibodies do occur occasionally—in low titre in patients with cancer and no neurological syndrome, and very infrequently in patients without identifiable tumour although this may reflect insufficient follow-up. An atypical antineuronal antibody is present in some cases of Sjogren’s syndrome.

Paraneoplastic cerebellar degeneration is associated with a variety of antibodies.

Anti-Purkinje cell antibodies (PCA1, or anti-Yo) are virtually always associated with breast or genital tract cancer, occasionally adenocarcinoma from other sites (Fig. 4) (Peterson et al. 1992). There have been a few cases with PCA1 antibodies but no tumour was identified on extended follow up, but this may be just a matter of time. These antibodies are not found in other cerebellar diseases.

Anti-Tr antibodies are found in some patients with Hodgkin’s lymphoma (Peltola et al. 1998; Graus et al. 2001). There are other cases of lymphoma where no antibody is identified.

PCA2 antibodies are rarer, but can be found in some patients with small cell lung cancer and cerebellar degeneration or limbic encephalitis (Vernino & Lennon 2000).

ANNA-1 (anti-Hu) is found in small cell lung cancer with cerebellar degeneration, where it is the presenting feature of a more generalized paraneoplastic encephalomyelitis.

The other antibodies are rarer and usually associated with opsoclonus, myoclonus and ataxia (ANNA-2), encephalitis (anti-CV2) or brainstem syndromes (anti-Ma).

Overall, nine out of ten patients with paraneoplastic cerebellar degeneration have a tumour of lung, breast, ovary or female genital tract, or lymphoma.
Opsoclonus, myoclonus and ataxia ANNA-2 (anti-Ri) is commonly found in OMA with rigidity akin to the stiff man syndrome, usually with breast and pelvic malignancies (Luque et al. 1991; Casado et al. 1994). ANNA-1 (anti-Hu) is almost always associated with small cell lung cancer (Hersh et al. 1994). PCA 1 (anti-Yo) is commonly associated with breast and pelvic malignancies (Honnorat et al. 1997). Anti-amphiphysin 1 is associated with small cell lung cancer (Saiz et al. 1999). Anti-neuronal antibodies in the serum of an adult can also be present in idiopathic non-paraneoplastic OMA, but this is uncommon. Conversely not all cases of paraneoplastic OMA have paraneoplastic antibodies. Children are almost always antibody negative.

Paraneoplastic retinopathy. Most patients have an antibody to the calcium binding protein, recoverin (anti-CAR antibody) (Fig. 5) (Grunwald et al. 1985). Virtually all with anti-CAR antibodies have small cell lung cancer (Jacobson et al. 1990). Some patients with melanoma associated retinopathy have antibipolar cell antibodies (Weinstein et al. 1994). There are case reports of antibodies to various other retinal proteins e.g. retinal enolase antibody but there are also patients who do not have antibodies yet have a paraneoplastic retinopathy. Common associated tumours in antibody negative cases are small cell lung cancer, melanoma, non-small cell lung cancer, breast, ovary, prostate, gastric, colon and uterine cancer.

Paraneoplastic sensory neuropathy patients commonly have antineuronal nuclear antibody (ANNA-1 or anti-Hu, 50–70%); anti-amphiphysin (very rare); atypical antibodies (rare) or they are antibody negative (30–40%). More than 90% of patients with paraneoplastic sensory neuropathy have small cell lung cancer. Occasionally breast, ovary, uterine carcinoma and lymphoma have been described.

Motor neuropathy. M-Protein is occasionally found, which may reflect association with multiple myeloma, and rarely ANNA-1 (anti-Hu) is found and is associated with small cell lung cancer.

Lambert-Eaton myasthenic syndrome. High titres of antibodies against P/Q-type voltage gated calcium channel antibodies (VGCA) are found in 90% of patients. Negative antibodies do not exclude paraneoplastic associated LEMS. Low titre false positives can occur. Synaptotagmin antibodies are found in some cases. The identification of LEMS clinically with neuro-

**Figure 5** Immuno-histochemistry in a case of paraneoplastic retinal degeneration demonstrating antirecoverin antibody (anti-CAR) staining of retinal photoreceptor cells (arrow). (Western Blot demonstrated 23 kDa bands in serum confirming that the antibody was anti-CAR antibody).
physiological confirmation should stimulate the search for an underlying tumour, especially small cell lung cancer.

**IMPORTANT TESTS TO NARROW THE DIFFERENTIAL DIAGNOSIS OF PARANEPOPLastic SYNDROMES**

**Brain MRI** (with gadolinium) helps exclude tumour, malignant meningitis, viral encephalitis, CJD, abscess and stroke. In paraneoplastic encephalomyelitis and limbic encephalitis there is frequently cerebral atrophy. In limbic encephalitis the mesial temporal region is frequently abnormal. In paraneoplastic cerebellar degeneration there may be cerebellar atrophy, especially when the disease has been present for sometime.

**CSF.** In paraneoplastic syndromes affecting the CNS, the CSF may be normal but more commonly shows a mild lymphocytosis and a non-specific increase in protein, IgG and IgG index, sometimes with oligoclonal bands (30%). In chronic inflammatory demyelinating polyradiculopathy, the high CSF protein and normal white cell count help confirm the diagnosis.

**Electroencephalogram** helps exclude herpes simplex encephalitis, non-convulsive status and CJD. It may show slowing over the temporal lobes or frontally in limbic encephalitis and paraneoplastic encephalomyelitis.

**Electro-retinogram** is flat in most cases of paraneoplastic retinopathy even though vision may be retained. In melanoma-associated retinopathy the dark adapted B wave has reduced amplitude.

**Neurophysiology.** In paraneoplastic sensory neuropathy, nerve conduction usually confirms the sensory neuropathy with reduced amplitude of sensory nerve action potentials in the presence of normal motor amplitudes and conduction. In LEMS, electromyography will demonstrate reduced amplitude of the compound muscle action potential with single supramaximal stimulation; an increase after exercise (post-exercise facilitation); a decremental response to repetitive stimulation at 3 Hz; an incremental response > 200% at > 30 Hz; and increased jitter on single fibre EMG (Fig. 6).

**Tensilon test** is not usually necessary although it is sometimes positive in LEMS, but seldom dramatically. It may give some idea of how the patient might respond to pyridostigmine.

**Biopsies.** Brain biopsy is seldom indicated except perhaps in some antibody negative cases to exclude cerebral vasculitis or intravascular lymphoma. Sural nerve biopsy is very rarely needed to exclude vasculitis, demyelination or lymphomatous infiltration of the nerves. Muscle biopsy may exclude myositis or myopathy in the occasional difficult case.

**WHERE IS THE LIKELY PRIMARY SITE OF THE TUMOUR AND WHAT TESTS SHOULD BE DONE TO LOOK FOR IT?**

Many different tumours have been associated with the neurological paraneoplastic syndromes, by far the most common are small cell lung cancer, breast and ovarian carcinoma, and lymphoma (Table 2). Clinical examination should certainly include careful breast and chest examination, abdominal and rectal examination and a search for lymph nodes. In cases of paraneoplastic cerebellar degeneration, gynaecological examination should be performed by someone experienced. Investigations should include:

- Blood tests for prostate specific antigen, carcinoembryonic antigen and CA 125; these are sometimes helpful in progressive encephalomyelitis.
- Chest MRI/CT where lung cancer is suspected.
- Abdominal and pelvic MRI/CT in paraneoplastic cerebellar degeneration.
- Mammmography in cases of progressive cer-
ebellar degeneration or opsoclonus, myoclonus and ataxia
• Skeletal survey must be considered if myeloma is a possibility with a motor neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, or the Lambert–Eaton myasthenic syndrome.
• Bone marrow may also be required if myeloma is suspected.
• Bronchoscopy if there is a mass on chest imaging or the patient is ANNA-1 (anti-Hu) positive but the chest CT/MRI is negative
• Laparoscopy if imaging of the pelvis is positive, or mammography and pelvic imaging are negative but PCA-1 (anti-Yo) antibody is positive.
• Positron Emission Tomography (PET) can sometimes identify a primary site when all the above investigations are negative.

WHAT TREATMENT OPTIONS ARE THERE FOR PARANEOPLASTIC SYNDROMES?
Advice to patients and relatives
I believe the patient should be told that their neurological symptoms may be due to a very early underlying tumour and that the various investigations being performed are to find it. If the tests do not reveal an underlying tumour (a common occurrence), but other causes of the neurological syndrome have been excluded, this is somewhat reassuring. However, this does not exclude the possibility of a paraneoplastic cause. If the antibodies are positive, it is as well to say that you suspect a paraneoplastic cause even if the cancer has not been found. Explain that you may wish to repeat some of the tests in six months to a year. Although spontaneous recovery and response to treatment is uncommon, most patients want to try something, because the condition is generally devastating.

Symptomatic management
• A psychiatric opinion may be helpful and appropriate in the management of psychiatric symptoms.
• Symptomatic treatment of opsoclonus and myoclonus with clonazepam may be worthwhile. Valproate or piracetam are alternatives and here have been reported responses using thiamine (Nausieda et al. 1981). Some patients require labyrinthine sedatives and antiemetics.
• Lambert–Eaton myasthenic syndrome (LEMS) is treated with oral 3,4 diaminopyridine (DAP), which blocks potassium channels and prolongs action potentials, thus increasing the release of acetylcholine. This produces improvement in virtually all cases, irrespective of the aetiology. The usual starting dose is 20 mg/day increasing to 20 mg, three-to-four times per day, as necessary. Adverse effects include peripheral paraesthesia, abdominal cramps, diarrhoea, insomnia and – at high doses – epileptic seizures. If 3,4 DAP is not easily available, and the patient is moderately affected, pyridostigmine 60 mg, tds, initially along with probanthine 15 mg,

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<th>SITE OF CANCER</th>
<th>Limbic encephalitis</th>
<th>Paraneoplastic encephalomyelitis</th>
<th>Paraneoplastic cerebellar degeneration</th>
<th>Opsoclonus, myoclonus and ataxia</th>
<th>Paraneoplastic retinopathy</th>
<th>Paraneoplastic sensory neuropathy</th>
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tds, usually helps to some extent, but in my experience never gives complete control. The combination of 3,4 DAP and pyridostigmine is highly effective. Treatment with 3,4 DAP for paraneoplastic LEMS is usually required for life, unless there is resolution of LEMS after treatment of the tumour (occasionally) or immunosuppressants are later used to control the disease. Guanidine has been used with success but I worry about the myelosuppression and other potentially serious toxicity.

It is important to warn the patient and others about sensitivity to muscle relaxant anaesthetics, and that LEMS may worsen with aminoglycoside and fluoroquinolone antibiotics, certain cardiac drugs (betablockers, calcium channel blockers, procainamide) and iodine based contrast agents.

**Later management**

**Immunological treatment** is justified when the diagnosis of a paraneoplastic syndrome is likely - characteristic presentation and paraneoplastic antibody positive; known cancer, characteristic presentation but paraneoplastic antibody negative; characteristic presentation, other diagnoses excluded and paraneoplastic antibody negative.

Firstly, iv methylprednisolone 1 g/day for three days, followed by oral steroids for a period, is worth trying as there have been some reports of improvement.

The paraneoplastic syndromes affecting the central nervous system are associated with intrathecal production of antibodies in most cases and so removal of the antibody from the blood rarely leads to any recovery. There are however, occasional cases reported of response and we have had experience of this in an early diagnosed case of cerebral ataxia (Counsell et al. 1994). I suggest IVIg 0.4 mg/kg/day for 5 days, repeated after 4–6 weeks.

The antibody production in paraneoplastic syndromes affecting the peripheral nervous system is not protected by the blood-brain barrier and so plasmapheresis or intravenous immunoglobulin can result in clinical improvement in, for example, the Lambert–Eaton myasthenic syndrome. In general the paraneoplastic syndromes may be slow to respond and any response may be delayed (Counsell et al. 1994; Uchuya et al. 1996; Blaes et al. 1999; Guy & Aptsiauri 1999; Bataller et al. 2001).

**Cyclophosphamide** alone or in combination with other immunosuppressants has been reported to improve some paraneoplastic syndromes (Keime-Guibert et al. 2000).

**Treatment of the underlying tumour** is indicated where a tumour has been identified. Patients with peripheral nervous system paraneoplastic syndromes and those associated with Hodgkin's disease are perhaps most likely to respond. Response has been noted in cases irrespective of whether the antibodies are present.

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**Despite their clinical variety, there are a number of generalizations around the paraneoplastic syndromes:**

- They present acutely or subacutely with progression over days to weeks.
- Most patients are not known to have cancer at presentation but, if they are, the cancer is usually rather limited in extent.
- The clinical presentation and the identification of serum antibodies help predict the likely tumour site in the majority of cases.
- Cancer may take weeks to 5 years to become evident in some patients with positive serum paraneoplastic antibodies.
- Disability is severe in most cases.
- Neurological symptoms and signs are occasionally partially responsive to immunological treatments, or treatment of the underlying tumour.
- Early identification of cancer and subsequent treatment may improve survival.
REFERENCES


