Leader

Neurological paraneoplastic syndromes

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Abstract

Paraneoplastic neurological syndromes are uncommon, however, their diagnosis is of major practical importance. The identification of antibodies in the serum or cerebrospinal fluid in central nervous system paraneoplastic syndromes confirms the clinical diagnosis of a paraneoplastic syndrome and allows early identification of an underlying tumour at a stage when it is localised and more amenable to treatment. The failure to identify antibodies in patients with characteristic presentations of underlying neurological paraneoplastic syndromes does not exclude an underlying cancer. Necrotising myelopathy, dermatomyositis, and chronic inflammatory demyelinating polyneuropathy all occur more frequently than expected in patients with cancer but autoantibodies have not yet been identified. Although significant advances have been made in diagnosis, further research is needed in the detection of autoantibodies and the elucidation of their role in the aetiology of neurological disease.

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Neurological complications of systemic cancer are very common (fig 1) and may be due to direct involvement from cancer or non-metastatic complications. The term paraneoplastic neurological syndrome is used to describe a group of well defined non-metastatic conditions that probably have an autoimmune basis. Paraneoplastic syndromes exclude cancer related vascular disease, infections, metabolic or nutritional disease, and complications of treatment.

Neurological paraneoplastic syndromes affect fewer than 1% of all cancer patients but they are important because the neurological syndrome is often severe and precedes the identification of the cancer in about 50% of cases.¹ Identification of the syndrome may allow diagnosis at a time when the primary tumour is small and localised and therefore more amenable to treatment. Recognition of specific neurological paraneoplastic syndromes helps focus the search for particular cancers, and identification of antibodies helps to confirm the diagnosis.

Aetiology

The aetiology of paraneoplastic syndromes is uncertain but an immune related mechanism is the most plausible. The evidence for a direct

Figure 1 Causes of neurological disorders related to neoplasia. LEMS, Lambert-Eaton myasthenic syndrome.

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Table 1 Common paraneoplastic syndromes affecting the nervous system

Syndrome	Terminology		
	Immunohistochemistry	Western immunoblot	Common tumour site
<i>Brain and cranial nerves</i>			
Limbic encephalitis or encephalomyelitis	ANNA-1	35–38 kDa	Lung (Hodgkin's)
Subacute cerebellar degeneration			
A	APCA	34, 62 kDa	Gynaecological, breast, lung
B	ANNA-1	35–38 kDa	Lung
C	Negative	Negative	Hodgkin's disease
Opsoclonus-myoclonus-ataxia	ANNA-2	55, 80 kDa	Neuroblastoma (children)
Photoreceptor degeneration	ANNA-1	47 kDa	Breast, lung (adults)
			Lung
<i>Dorsal root ganglia</i>			
Subacute sensory neuronopathy	ANNA-1	35–38 kDa	Lung
<i>Peripheral nerves</i>			
Acute inflammatory demyelinating polyneuropathy	Uncertain	Uncertain	Hodgkin's, adenocarcinoma, osteosclerotic myeloma
Chronic inflammatory demyelinating polyneuropathy	Uncertain	Uncertain	Hodgkin's, adenocarcinoma, osteosclerotic myeloma
<i>Neuromuscular junction and muscle</i>			
Lambert-Eaton myasthenic syndrome	Voltage gated calcium channel antibody		Lung, prostate, cervix
Dermatomyositis	Uncertain	Uncertain	Breast, ovary, lung, lymphoma

autoimmune basis is strongest for Lambert-Eaton myasthenic syndrome (LEMS).² Voltage gated calcium channel antibodies have been identified in the serum of patients with LEMS, and passive transfer of IgG from affected patients induces the disorder in experimental animals.^{2,3} Voltage gated calcium channel antibodies bind to the presynaptic calcium channels of the neuromuscular junction, disrupting the structure of the channels, and causing failure of release of calcium in response to an action potential that results in a reduction in acetyl choline release.³

Paraneoplastic syndromes involving the central nervous system probably also have an autoimmune basis as they are associated with serum autoantibodies. It is likely that the patient's immune system recognises a tumour related antigen as foreign and produces an antibody response. The antibody cross reacts with shared antigens or epitopes in the central nervous system and may result in a paraneoplastic neurological syndrome. Despite the association of autoantibodies with central nervous system paraneoplastic neurological syndromes (table 1) passive transfer of immunoglobulin from patients with paraneoplastic central nervous system disease to experimental animals does not reproduce the clinical syndrome or result in pathological changes. Furthermore, immunisation of mice with paraneoplastic antigen does not produce any clinical or pathological changes.⁴

Terminology

The terminology used to describe paraneoplastic antibodies has been the subject of heated controversy. Some groups favour a descriptive generic nomenclature—that is, anti-Purkinje cell antibody (APCA), antineuronal nuclear antibody type 1 (ANNA-1), and antineuronal nuclear antibody type 2 (ANNA-2) based on immunohistochemistry alone, while others favour the case for an antibody and antigen specific nomenclature (anti-

Yo, anti-Hu, and anti-Ri) determined by a combination of immunohistochemistry and western immunoblotting.^{5,6}

An international symposium on the topic developed consensus guidelines for the detection of paraneoplastic antineuronal specific antibodies.⁷ The consensus opinion is that the two terminologies are not interchangeable as immunohistochemistry alone is not sufficiently specific. If antibody is detected in serum or cerebrospinal fluid (CSF) using immunohistochemistry alone the result should be referred to as APCA or ANNA depending on immunohistochemical findings. ANNA antibody may be associated with Sjogren's syndrome as well as other autoimmune conditions, whereas anti-Hu is more specific for underlying neoplasia, usually small cell lung cancer.⁸ The finding of anti-Hu or anti-Yo in serum or CSF (at a dilution of >1:500 and >1:50, respectively) by immunohistochemistry and western immunoblotting has a specificity of greater than 95% for a paraneoplastic neurological syndrome.⁹ Some patients who have small cell lung cancer without neurological symptoms may harbour low titres of anti-Hu antibody that can only be detected by western immunoblotting using high affinity purified recombinant proteins.¹⁰ An outline of methods used in immunohistochemistry and western blotting is given below; further details are available elsewhere.^{6,7,10}

Classification

A useful clinical classification divides the neurological paraneoplastic syndromes according to their anatomical level: brain and cranial nerves, spinal cord and dorsal root ganglia, peripheral nerves, neuromuscular junction, and muscle (table 1).¹

PARANEOPLASTIC ENCEPHALOMYELITIS

This condition is found in around three of every 1000 cancer patients and can present with a variety of clinical features: seizures, subacute dementia, and personality change

Figure 2 Indirect immunoperoxidase staining. (A) Cerebral cortex section with control serum (1/500 dilution). (B) Cerebral cortex section with serum from a patient with limbic encephalitis and small cell lung cancer (1/500 dilution). Neuronal nuclear staining with faint staining seen in cytoplasm and axons.

(limbic encephalitis), subacute cerebellar signs, and autonomic dysfunction.¹¹ Paraneoplastic encephalomyelitis has been reported with various other paraneoplastic syndromes such as brainstem encephalitis, sensory neuronopathy, and painless visual loss due to paraneoplastic optic neuritis. Cancer associated spinal cord disease is usually metastatic but when paraneoplastic in origin usually occurs in conjunction with paraneoplastic encephalomyelitis. Examples of paraneoplastic spinal cord disease include necrotising myelopathy and myelitis.

Magnetic resonance imaging of the brain is usually normal in paraneoplastic encephalomyelitis but it may demonstrate temporal lobe atrophy or high signal changes in the temporal lobes on T2 weighted images.¹²

The associated antibody (ANNA-1/anti-Hu) reacts with a neuronal nuclear antigen that belongs to a family of RNA binding proteins and is present in higher concentrations in CSF than serum.¹³ Identification of anti-Hu antibodies (by immunohistochemistry and western immunoblot) at a concentration greater than 1/500 in serum is highly specific for a paraneoplastic neurological syndrome and 80% of patients with this finding will have small cell lung cancer.

Patients tend to be middle aged and both sexes are equally affected, although those who have anti-Hu antibody are more commonly female. The anti-Hu antibody may also be present in low titres in patients with small cell lung cancer without encephalomyelitis and these patients tend to be female with less extensive malignant disease.¹⁰ Other cancers associated with encephalomyelitis include

breast, gynaecological, and gastrointestinal cancers, and Hodgkin's disease.¹¹ Patients with encephalomyelitis or sensory neuronopathy who are antibody positive have a better prognosis than those in whom antibodies are not identified.¹ There are no other known antibodies associated with paraneoplastic brainstem encephalitis, optic neuritis or necrotising myelopathy. Necrotising myelopathy is associated with lymphomas, leukaemias, and cancer of the lung.

Pathological findings

The pathological process in paraneoplastic encephalomyelitis occurs diffusely throughout the central nervous system. Cases with and without anti-Hu antibody are indistinguishable.¹ Pathological findings are localised to the areas of the nervous system that are involved clinically.¹⁴ In limbic encephalitis there is perivascular lymphocytic cuffing, neuronophagia with microglial proliferation, and astrogliosis. Neuronal loss is most obvious in the limbic cortex and insula.¹⁴ The immunohistochemical staining pattern of ANNA-1/anti-Hu consists of strong staining of all central and peripheral nervous system neuronal nuclei with sparing of nucleoli and weaker granular cytoplasmic staining; no staining of systemic tissues occurs (fig 2).⁷ Necrotising myelopathy shows widespread necrosis throughout the spinal cord.

PARANEOPLASTIC CEREBELLAR DEGENERATION

Although perhaps the best known of the paraneoplastic neurological syndromes, paraneoplastic cerebellar degeneration is rare, occur-

Figure 3 Indirect immunoperoxidase technique. (A) Cerebellar section with control serum (1/500 dilution). (B) Cerebellar section with serum from a patient with paraneoplastic cerebellar ataxia and fallopian tube carcinoma (1/500 dilution). Intense staining of the cytoplasm of Purkinje cells and axons (APCA positive).

ring in two of every 1000 patients with cancer. There are about 300 cases reported in the literature. The clinical features are subacute pancerebellar dysfunction with truncal and limb ataxia, as well as dysarthria and nystagmus, which develops over weeks. There is often severe residual disability. Magnetic resonance imaging can show cerebellar atrophy in advanced cases.¹⁵ Paraneoplastic cerebellar degeneration can be categorised into four main subgroups that differ in prognostic significance and have different associated autoantibodies.¹

Associated with APCA/anti-Yo antibody—This occurs in middle aged women with occult ovarian or breast cancer that is usually indolent; the cerebellar disease often precedes identification of the cancer. Many cases are associated with high titres of serum ($> 1/500$) or CSF ($> 1/50$) antibodies that react with the Purkinje cells in the cerebellum (APCA-1/anti-Yo).¹⁶ The antigens belong to a family of DNA binding proteins.

Associated with ANNA-1/anti-Hu antibody—ANNA-1/anti-Hu antibody can be associated with cerebellar degeneration either in isolation or with encephalomyelitis.

Associated with Hodgkin's lymphoma—These patients are usually young men and the

cerebellar disease often follows the diagnosis of lymphoma. Spontaneous or treatment associated remissions are more common in this subgroup. Anti-Purkinje cell antibodies resembling but not identical to APCA-1/anti-Yo have been found in a small proportion of these patients at low titres.

Without antineuronal antibodies—Some cases of paraneoplastic cerebellar degeneration are associated with small cell lung cancer and may occur in association with LEMS.¹⁷ Some of these patients have voltage gated calcium channel antibodies.

Pathological findings

The pathological process in APCA/anti-Yo antibody positive patients is very site specific. There is severe loss of Purkinje cells throughout the cerebellum, with or without lymphocytic infiltration, with remaining cells showing axonal swelling.¹ There is atrophy of the granular and molecular layers with microglial proliferation and astrogliosis but relative sparing of basket cells. The deep cerebellar nuclei and the cerebellar connections to the brain stem are normal. Patients with APCA-1/anti-Yo antibody tend to show more inflammatory changes and characteristic immunofluorescence patterns with coarse granular staining of Purkinje cell cytoplasm as well as proximal axons and dendrites; nuclei and systemic tissues are not stained (fig 3).⁷ Cases of paraneoplastic cerebellar degeneration associated with ANNA-1/anti-Hu stain the cortical and cerebellar neuronal nuclei.

CANCER ASSOCIATED RETINOPATHY

Cancer associated retinopathy is a rare paraneoplastic condition that presents with episodic visual obscurations and loss of acuity with associated scotomata. Pathological findings include inflammatory infiltrates into both photoreceptor and ganglion cells and antibodies have been reported against antigens in both these types of cell.

OPSOCLONUS-MYOCLONUS-ATAXIA

Paraneoplastic opsoclonus is associated with myoclonus and truncal ataxia and onset is often acute.¹⁸ Immunohistochemistry of serum or CSF shows an antineuronal nuclear antibody (ANNA-2). The antibody, anti-Ri, is identical to ANNA-1 on immunohistochemical criteria but shows a different banding pattern with western immunoblotting. Western immunoblotting identifies bands at 55 and 80 kDa and this is referred to as ANNA-2/anti-Ri. The presence of antibody identifies a subset of patients with this syndrome, usually adults, who commonly have a breast or lung neoplasm although it can be associated with gynaecological malignancies. In half of the adult cases with this syndrome neurological symptoms and signs precede the diagnosis of malignancy. Children who present with opsoclonus-myoclonus-ataxia do not harbour the ANNA-2/anti-Ri antibody but are commonly found to have neuroblastoma.¹⁰

Pathological findings

Microscopic appearances described in some cases include mild perivascular inflammatory changes, loss of Purkinje cells, and abnormalities in the dentate nuclei.^{18 20} Immunohistochemistry patterns of anti-Ri include strong staining of only central nervous system neuronal nuclei, sparing of nucleoli, weak granular cytoplasmic staining, and no staining of systemic tissues.⁷

PARANEOPLASTIC SUBACUTE SENSORY
NEURONOPATHY (DORSAL ROOT
GANGLIONOPATHY)

This paraneoplastic syndrome occurs in around seven of every 1000 cancer patients. Although it is probably the most common paraneoplastic neurological syndrome it is probably under recognised. Patients present with pure sensory loss developing over weeks to months and involving all modalities. It can involve either upper or lower limbs and can rarely present in the face.¹ It precedes identification of the cancer in the majority of cases and the occult tumour is usually small cell lung cancer.²¹

Pathological findings

Abnormalities are found in the dorsal root ganglia with infiltration by lymphocytes and macrophages. In longstanding symptomatic patients there is neuronal loss and capsular cell proliferation, but little in the way of inflammation. Secondary axonal degeneration occurs in the dorsal nerve roots, peripheral sensory nerves, and posterior columns of the spinal cord. The lateral and anterior columns are well preserved.²²

LAMBERT-EATON MYASTHENIC SYNDROME

LEMS occurs in around two of every 1000 cancer patients and is characterised by limb weakness, usually of the lower limbs, and is commonly associated with autonomic dysfunction.¹ The deep tendon reflexes are reduced but show facilitation after exercise. Sixty per cent of all cases are associated with an underlying malignancy and in 40% the LEMS occurs as an autoimmune condition in its own right. Non-paraneoplastic cases of LEMS occur more commonly in middle aged women. When cancer is identified it is usually small cell lung cancer, although cancer of the prostate or cervix have been described. Antibodies against voltage gated calcium channels are present in most patients. Electromyography shows characteristic changes of a decrement in compound muscle action potential amplitude with low rates of repetitive stimulation (2–10 Hz) and an increment with high rates (20–40 Hz).²³

Pathological findings

Muscle biopsy changes are non-specific using light microscopy. Electron microscopic techniques are much more helpful and demonstrate hypertrophy of the postsynaptic membrane with atrophy of the terminal axons and increased branching of nerve terminals.²⁴

Treatment of paraneoplastic syndromes

In the vast majority of cases paraneoplastic syndromes are refractory to any form of treatment. Spontaneous remission of neurological symptoms can occur in patients with opsoclonus-myoclonus-ataxia and very rarely in limbic encephalitis and paraneoplastic cerebellar degeneration.¹ Symptoms of LEMS can show clinical improvement following oral treatment with 3,4-diaminopyridine. There is increasing evidence that if paraneoplastic syndromes can be proved early in the course of the disease, treatment directed at the immune response (for example, intravenous immunoglobulin, plasmapheresis, immunosuppression) or at the underlying tumour (surgery, radiotherapy, chemotherapy) can halt or even reverse the neurological syndrome. Thiamine and clonazepam may be helpful in some cases of paraneoplastic cerebellar degeneration and immunoadsorption has been of benefit in paraneoplastic opsoclonus.²⁵

Conclusion

Although paraneoplastic neurological syndromes are uncommon their diagnosis is of major practical importance. The identification of antibodies in the serum or CSF in central nervous system paraneoplastic syndromes confirms the clinical diagnosis and allows early identification of an underlying tumour at a stage when it is localised and more amenable to treatment. Identification of antibodies may be of prognostic importance as the presence of certain antibodies are associated with a good response to treatment of the underlying cancer.²⁶ The failure to identify antibodies in patients with characteristic presentations of underlying neurological paraneoplastic syndromes does not exclude an underlying cancer. Necrotising myelopathy, dermatomyositis, and chronic inflammatory demyelinating polyneuropathy all occur more frequently than expected in patients with cancer but autoantibodies have not yet been identified using current techniques. Although significant advances have been made in diagnosis, further research is needed in the detection of autoantibodies and the elucidation of their role in the aetiology of neurological disease.

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- 1 Posner JB. Neurologic complications of cancer. *Contemporary neurology series*: 45. Philadelphia, 1995:353–85.
- 2 Lang B, Newsom-Davis J, Wray D. Autoimmune aetiology for Eaton-Lambert myasthenic syndrome. *Lancet* 1981;i: 224–6.
- 3 Rosenfeld MR, Wong E, Dalmau J, *et al*. Cloning and characterisation of a Lambert-Eaton myasthenic syndrome antigen. *Ann Neurol* 1993;33:113–20.
- 4 Sillevs Smitt PAE, Manley GT, Posner JB. Immunisation with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice. *Neurology* 1995; 5:1873–8.
- 5 Lennon VA. Paraneoplastic autoantibodies: the case for a descriptive generic nomenclature. *Neurology* 1994;44: 2236–40.
- 6 Dalmau J, Posner JB. Neurologic paraneoplastic antibodies (anti-Yo; anti-Hu; anti-Ri): case for a nomenclature based on antibody and antigen specificity. *Neurology* 1994;44: 2241–6.
- 7 Moll JWB, Antoine JC, Brashear HR, *et al*. Guidelines for the detection of paraneoplastic antineuronal-specific antibodies: report from the workshop to the fourth meeting of the International Society of Neuroimmunology on Paraneoplastic Neurological Disease, 22–23 October 1994, Rotterdam, the Netherlands. *Neurology* 1995;45:1937–41.

- 8 Moll JWB, Markusse HM. Antineuronal antibodies in patients with neurological complications of primary Sjogren's syndrome. *Neurology* 1993;43:2574-81.
- 9 Twijnstra A, Keyser A, Ongerboer de Visser BW. *Neuro-oncology—primary tumours and neurological complications of cancer*. Amsterdam: Elsevier, 1993.
- 10 Dalmau J, Furneaux HM, Gralla RJ, Kris MG, Posner JB. Detection of anti-Hu antibody in serum of patients with small cell lung cancer; a quantitative western blot analysis. *Ann Neurol* 1990;27:544-52.
- 11 Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. *Medicine* 71;2:59-71.
- 12 Lacomis D, Khosbin S, Schich RM. Magnetic resonance imaging of paraneoplastic limbic encephalitis. *J Comput Assist Tomogr* 1990;14:115-17.
- 13 Furneaux HM, Reich L, Posner JB. Autoantibody synthesis in the CNS of patients with paraneoplastic syndromes. *Neurology* 1990;40:1085-91.
- 14 Dalmau J, Furneaux HM, Rosenblum MK. Detection of anti-Hu antibody in specific regions of the nervous system and tumour from patients with paraneoplastic encephalomyelitis and sensory neuropathy. *Neurology* 1991;41:1757-64.
- 15 Greenberg HS. Paraneoplastic cerebellar degeneration; a clinical and CT study. *J Neurooncology* 1984;2:337-82.
- 16 Hetzel DS, Stanhope CR, O'Neil GP. Gynaecological cancer in patients with subacute paraneoplastic cerebellar degeneration predicted by APCA antibodies and limited in metastatic volume. *Mayo Clin Proc* 1982;57:15-21.
- 17 Blumenfeld AM, Recht LD, Chad DA. Coexistence of Lambert-Eaton myasthenic syndrome and paraneoplastic cerebellar degeneration; differential effects of therapy. *Neurology* 1991;41:1682-5.
- 18 Luque FA, Furneaux HM, Posner JB. Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. *Ann Neurol* 1991;29:241-51.
- 19 Ridley A, Kennard C, Scholtz CL. Omnipause neurones in two cases of opsoclonus associated with oat-cell carcinoma of the lung. *Brain* 1987;110:1699-709.
- 20 Ross AJ, Zeman W. Opsoclonus, adult cancer and chemical pathology in the dentate nuclei. *Arch Neurol* 1967;17:546-51.
- 21 Graus F, Elkon KB, Cordon-Cardo C, Posner JB. Sensory neuronopathy and small cell lung cancer. *Am J Med* 1986;80:45-52.
- 22 Anderson NE, Cunningham JM, Posner JB. Autoimmune pathogenesis of paraneoplastic neurological syndromes. *Crit Rev Neurobiol* 1987;3:245-99.
- 23 Lambert EH. Defects of the neuromuscular junction in syndromes other than myasthenia gravis. *Ann NY Acad Sci* 1966;135:367-84.
- 24 Fukuhara N, Takamori M, Gutmann L, Chow SM. Eaton Lambert syndrome. Ultrastructural study of motor end plates. *Arch Neurol* 1972;27:67.
- 25 Nausieda PA, Tanner CM, Weiner WJ. Opsoclonic cerebellopathy: a paraneoplastic syndrome responsive to thiamine. *Arch Neurol* 1981;38:780-1.
- 26 Graus F, Dalmau J, Rene R, Tora M, *et al*. Anti-Hu antibodies in patients with small cell lung cancer: association with complete response to therapy and improved survival [abstract]. *J Neuro-Onc* 1996;30:129.

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