Paraneoplastic neurological syndromes

Introduction

Almost any part of the nervous system can be affected by paraneoplastic syndromes (table 1). It is important to recognise paraneoplastic neurological syndromes (PNS), for several reasons. They usually predate symptoms of the malignancy, and identification should lead to a search for the primary tumour. PNS may also predate the clinical appearance of metastatic deposits or tumour recurrence. In a patient with a diagnosed malignancy there is a tendency to consider effects at remote sites to be considered as secondary deposits, and the patient may be deprived of appropriate therapy owing to an incorrect diagnosis of multiple secondary deposits. Most of the PNS are of immunological aetiology, but immuno-suppression is not beneficial except in a few. Appropriate treatment for the primary tumour usually helps in improving the PNS symptoms.

Pathogenic mechanisms

Many non-neurological paraneoplastic syndromes are due to the effects of hormones or peptides produced by the tumour. But PNS are commonly immune mediated. Ectopic expression of neural antigens by the tumour gives rise to formation of antibodies against them. These in turn attack the neural tissues through humoral or T-cell mediated mechanisms. Cerebrospinal fluid (CSF) analysis may show evidence of intrathecal immunoglobulin synthesis. And tumours which give rise to PNS are often infiltrated with inflammatory cells making identification difficult.

Table1. **Paraneoplastic syndromes affecting different sites of the nervous system**

Muscle	
	Polymyositis or dermatomyositis
	Necrotising myopathy
	Myotonia
	Polymyalgia rheumatica
Neuromuscular junction	
	Myasthenia gravis
	Lambert-Eaton myasthenic syndrome
Peripheral nerves	
	Polyneuropathy or radiculopathy (Guillain-Barre syndrome)
	Plexopathy (brachial neuritis)
	Chronic sensory motor neuropathy
	Autonomic neuropathy
	Vasculitic neuropathy
	Neuromyotonia
Anterior horn cells	
	Amyotrophic lateral scleroisis
	Stiff-man (stiff-person) syndrome
Dorsal root ganglia	
	Sensory neuronopathy
Spinal cord	
	Nectrotising myelopathy
	Transverse myelitis
	Subacute motor neuronopathy
Cerebellar	
	Cerebellar degeneration (Subacute cerebellar ataxia)
Brain	
	Limbic encephalitis
	Brainstem encephalitis
	Opsoclonus myoclonus
Cranial nerves	
	Retinopathy

A cause and effect relationship with antibodies is observed in some syndromes. Antibodies against P/Q type voltage-gated calcium channels in myasthenic myopathic (Lambert-Eaton) syndrome can explain the preganglionic block at the neuromuscular junction with muscle weakness. Anti-acetylcholine receptor antibodies in myasthenia gravis and antibodies against voltage-gated potassium channels in neuromyotonia are other examples. In many PNS affecting the brain the cause and effect relationship cannot be directly demonstrated although there is evidence of inflammation.

Diagnosis

Clinical features of PNS are not particularly different from similar syndromes due to non-paraneoplastic causes. Some clues such as the time course of cerebellar degeneration and severe pain with neuropathy may raise suspicion but are not useful in themselves for accurate diagnosis.

CSF analysis gives a clue to immunological aetiology in the nervous system eg. an oligoclonal band and pleocytosis. Results of the neurophysiological investigations such as electromyography (EMG), nerve conduction studies, repetitive stimulation and single fibre EMG are useful in confirming the clinical syndrome but do not support a paraneoplastic aetiology. Magnetic resonance imaging (MRI) may show structural changes in limbic encephalitis and changes of cerebellar atrophy within a few months.

Detection of paraneoplastic antibodies helps to diagnose PNS. Most of the antibodies are present in serum, hence detection in the CSF is not essential. As shown in table 2 some antibodies are specific for tissues regardless of the aetiology of the PNS. Myasthenia gravis and myasthenic syndrome can occur without an association with PNS. Sometimes the presence of antibodies is a strong pointer to a PNS aetiology, as in the case of anti-Hu antibodies.

If antibodies are detected investigations can be focused on the likely organs (see table 2).

In the absence of clues from clinical examination and antibody tests, high resolution CT scan of the chest, abdomen and pelvis, whole body fluorodeoxyglucose positron emission tomography (FDG-PET), PET/CT, mammography, testicular ultrasonography and MRI may be useful. If all are negative, review at every 3 months for up to 3 years is recommended.

Diagnostic criteria

Because of the difficulties in diagnosis patients with suspected PNS may be classified as “definite” and “probable”.

Table 2. **Antibodies associated with paraneoplastic neurological syndromes**

Antibodies	*Clinical syndrome*	*Associated cancer*
Acetylcholine receptor antibodies(Anti-AChR)	Myasthenia gravis	Thymoma
Anti-nAchR	Paraneoplastic autonomic neuropathy	SCLC*
Antibodies against voltage-gated calcium channels (Anti-VGCC)	Lambert-Eaton myasthenic syndrome (LEMS)	SCLC
Antibodies against voltage-gated potassium channels (Anti-VGKC)	Neuromyotonia, limbic encephalitis	Thymoma, SCLC
Antibodies against cytoplasm of Purkinje cells Anti-Yo (PCA1)	Subacute cerebellar degeneration	Ovarian, breast and lung cancers
(PCA2)	Subacute cerebellar degeneration, encephlaomyelitis	SCLC
Anti-neuronal nuclear antibody Anti-Hu (ANNA 1)	Encephalomyelitis, limbic encephalitis, sensory neuronopathy, cerebellar degeneration, autonomic neuropathy	SCLC, prostate cancer, neuroblastoma
Anti-Ri (ANNA 2)	Opsoclonus-myoclonus, brainstem encephalitis, ataxia	Breast, ovary, bladder
ANNA 3	Encephalomyelitis, sensory neurnopathy	SCLC
Anti Ma-1	Limbic encephalitis, brainstem encephalitis, subacute cerebellar degeneration	Testicular cancer
Anti-amphiphysin	Stiff person syndrome, encephalomyelitis, sensory neuronopathy, sensory motor neuropathy	Breast, SCLC
Anti-Tr (PCA-Tr)	Subacute cerebellar degeneration	Hodgkin lymphoma
Anti-mGlu R1	Subacute cerebellar degeneration	Hodgkin lymphoma
Anti-recovering	Retinopathy	SCLC, melanoma, gynaecological cancers

* SCLC = small cell lung cancer

Table 3. **Symptomatic paraneoplastic neurological syndromes**

Syndrome	*Clinical features*	*Associated tumors*
Limbic encephalitis	Subacute confusion, short term memory loss, psychiatric symptoms related to limbic system, seizures, hyperthermia and endocrine abnormalities due to hypothalamic involvement	SCLC, testicular tumours, breast cancers, Hodgkin disease and thymoma
Brainstem encephalitis	Diplopia, dysarthria, dysphagia, gaze abnormalities; nuclear or internuclear, facial numbness, subacute hearing loss	SCLC
Subacute cerebellar ataxia	Nausea, vomiting, dizziness, developing rapidly with dysarthria, gait abnormalities and incoordination	SCLC, ovarian malignancy, Hodgkin lymphoma
Opsoclonus-myoclonus	Involuntary arrhythmic, high amplitude, gross conjugate saccades in all directions, no remission in darkness or with eye closure, remissions and relapses, increased startle reaction	SCLC, breast, ovarian, neuroblastoma (in children), thyroid, bladder
Necrotizing myelitis	Paraparesis with sphincter involvement, which is rapidly ascending to involve the brainstem	
Subacute sensory neuronitis	Rapidly progressing and disabling pain, paraesthesia, clumsiness and unsteady gait, asymmetrical or multifocal sensory loss of face and abdomen, sensory loss for all modalities, absent tendon reflexes	SCLC, breast, ovarian sarcoma Hodgkin lymphoma
Encephalomyelitis	Features of limbic encephalitis, brainstem encephalitis, cerebellum, myelitis and the sensory neuronitis	SCLC
LEMS	Proximal muscle weakness, dry mouth, autonomic dysfunction, absent reflexes which get augmented after isotonic contraction or repeated tapping	SCLC (without PNS also reported)
Dermatomyositis	Heliotropic rash, proximal muscle weakness and pain, arthralgia, myocarditis	Ovary, colorectal, gastric, breast, pancreas, non-Hodgkin lymphoma
Neuromyotonia (peripheral nerve hyperexcitability)	Cramps, fasciculations, motor weakness, hyperhydrosis, EMG fibrillations, myokimic discharges	Thymoma, SCLC

Definite PNS

a. A classical syndrome (eg. LEMS, dermatomyositis), with cancer developing within 5 years of the diagnosis of PNS.

b. A non-classical syndrome which does not remit spontaneously, but objectively improves or resolves after cancer treatment.

c. A non-classical syndrome with paraneoplastic antibodies, and cancer that develops within 5 years of the diagnosis of PNS.

d. A neurological syndrome (classical or not) with well-characterized paraneoplastic antibodies.

Probable PNS

a. A classical syndrome without paraneoplastic antibodies and no cancer but at high risk to have an underlying tumour (eg. heavy smoker).

b. A neurological syndrome (classical or not) without cancer but with partially characterised paraneoplastic antibodies.

c. A non-classical neurological syndrome, with no paraneoplastic antibodies, but cancer that presents within 2 years of the neurological syndrome.

Clinical features

Symptomatic PNS are rare. They include LEMS (3% of SCLC), myasthenia gravis (15% of thymoma), and demyelinating peripheral neuropathy (10% of myeloma with monoclonal gammopathy and nearly 50% of osteoclastic myeloma). If routine electrophysiological studies are included in evaluation the proportion of patients with PNS is likely to be higher. Clinical features and electrophysiological abnormalities of some syndrome are listed in table 3.

Treatment

As the pathogenic mechanisms are immune mediated removing the antigenic source (ie. the tumour), and immunosuppression, or removing the antibodies should be effective. Removal of primary tumour is effective. Immunosuppression is known to be effective only in a few syndromes such as myasthenia gravis, LEMS and stiff-person syndrome. In myasthenia gravis and LEMS, plasma exchange and immunoglobulin are effective. In T-cell mediated diseases such as subacute cerebellar degene-ration and encephalomyelitis tacrolimus or mycophenolate mofetil can be tried. Dermatomyositis can be treated with steroids and azathioprine. Although there are no standard protocols for immunotherapy for PNS many physicians combine plasma exchange, immuno-globulins, steroids and other immunosuppressives when the clinical condition deteriorates.

Symptomatic treatment may be beneficial in some syndromes. In myasthenia gravis pyridostigmine or neostigmine are beneficial whereas in neuromyotonia, phenytoin sodium may help.

Prognosis

PNS like myasthenic syndrome responds well to immunosupression and removal of tumour. Peripheral neuropathy due to osteoclastic myeloma improves with radiotherapy. Opsoclonus myoclonus responds to tumour removal or immunosupression or both. The prognosis of encephalomyelitis is poor but there may be some response to tumour removal.

The differences in prognosis and response to treatment can be explained on the underlying pathogenic mechanisms. In LEMS there is no neuronoal loss although the function of the nerve is blocked. In encephalitis there is neuronal cell damage caused by intracellular antibodies.

Further reading

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