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ESSENTIALS Paraneoplastic neurological syndromes are disorders caused by the presence of an underlying tumour, but not due to either direct or metastatic invasion, or to recognized metabolic or endocrine com- plications. They are thought to arise from an autoimmune response to ‘onconeural’ tumour antigens which are also expressed by cells of the central or peripheral nervous systems. Paraneoplastic neurological syndromes are rare but important be- cause (1) they often develop before the cancer has been identified, (2) serological testing for specific antineuronal (onconeural) anti- bodies may identify a neurological disorder as paraneoplastic and the results may suggest the location of the underlying tumour and/ or predicts its prognosis. In some cases, the identity of the antibody predicts an immunotherapy-responsive disease. Epidemiology—the most common tumours associated with paraneoplastic syndromes are lung (both small-cell lung cancer and non-small-cell lung cancer), ovary, breast, thymus, lymph nodes (Hodgkin’s disease and non-Hodgkin’s lymphoma) and testis. Treatment—a few paraneoplastic syndromes respond to immuno- suppression or to treatment of the underlying cancer, particularly when they are associated with germ cell tumours and antibodies to neuronal cell-surface proteins, but treatment is unrewarding for most. Patients with paraneoplastic neurological syndromes often re- main severely disabled even if the cancer is cured. Specific syndromes Brain—(1) cerebellar degeneration—most common with lung cancer (especially small-cell lung cancer), breast, and gynaecological cancer, and Hodgkin’s disease; (2) opsoclonus/myoclonus; (3) limbic en- cephalitis (see Chapter 24.24); (4) brainstem encephalitis; Spinal cord, dorsal root ganglia, and peripheral nerves—(1) necro- tizing myelopathy; (2) motor neurone disease (some cases); (3) mye- litis; (4) sensory neuronopathy; (5) peripheral neuropathies. Neuromuscular junction and muscle (see

also Chapter 24.18)—(1) Lambert–Eaton myasthenic syndrome—typically associated with small-cell lung cancer; (2) myasthenia gravis—occurs in 30% of patients with thymomas; (3) polymyositis/dermatomyositis; (4) neuromyotonia. Incidence The most frequent paraneoplastic neurological syndrome (PNS) is Lambert–Eaton myasthenic syndrome (LEMS), which affects about 2 to 3% of patients with small-cell lung cancer (SCLC), and myasthenia gravis. This is most commonly autoimmune, but about 10% of patients have an associated thymoma (Chapter 24.18). By contrast, the PNS affecting the central nervous system are very rare, probably affecting fewer than 1% of patients with cancers of all types. In one series of almost 1500 patients with tumours, only three had paraneoplastic cerebellar degeneration, and none had subacute sensory neuronopathy. In a surveillance study of all PNS from the United Kingdom, 50 cases were iden- tified in one year; the female:male ratio was greater than 3:1, the median age of onset of PNS was 66 years and only 11% of patients were less than 50 years of age at presentation. The PNS preceded the diagnosis of cancer in 84% of patients. In a recent European multicentre study of almost 1000 patients, predominantly with central nervous system involvement, paraneoplastic cerebellar degeneration and sensory neuronopathy were the most fre- quent (24%), followed by limbic or brainstem encephalitis and encephalomyelitis (22%). Despite their low incidence, paraneoplastic syndromes are im- portant for several reasons. • About two-thirds of cases develop before the cancer has been identified and so their presence may lead to the detection of small and potentially curable cancers. • The presence of specific antibodies in the serum of patients with a PNS identifies the neurological disorder as paraneoplastic and may strongly suggest the location of the underlying tumour. • The PNS is often more disabling than the cancer and, in some instances, may be the cause of death. • A PNS or an antibody associated with a PNS (see next) may pre- dict a less aggressive course for the cancer. • Paraneoplastic antibodies identify proteins normally restricted to neurones that are of importance in the development and maintenance of the nervous system (see ‘Further reading’).
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24.23 Paraneoplastic neurological syndromes 6385 The syndromes The clinical syndromes may be focal or diffuse involving single or multiple parts of the nervous system. The most well-characterized syndromes (termed ‘classical’ by Graus et al.) are those that should always arouse suspicion of an associated cancer, and are listed in Table 24.23.1. These syndromes are commonly, but not always, associated with antibodies to certain onconeural antigens which point to the most likely tumours (Table 24.23.2), and will be described in detail next. The exception is limbic encephalitis that is often nonparaneoplastic (Chapter 24.24) and treatable with immunomodulation. Onconeural antibodies These antibodies often confirm the syndrome as being paraneoplastic and may point to a specific underlying tumour. For example, a pa- tient with paraneoplastic cerebellar degeneration who has serum anti-Yo antibodies will almost always have a breast, ovarian, or other gynaecological cancer. Patients with paraneoplastic cere- bellar degeneration associated with nongynaecological cancers have other antibodies that react with Purkinje cells or do not have antibodies identifiable by current techniques. The main antigens (Table 24.23.2) are cytoplasmic or nuclear proteins, although some are membrane proteins that are accessible to circulating antibodies, Table 24.23.1 Classical paraneoplastic neurological syndromes Syndromes Anatomical region Encephalomyelitis Limbic system, brainstem, spinal cord Limbic encephalitis Limbic system Subacute cerebellar degeneration Cerebellum Opsoclonus–myoclonus Brainstem Sensory neuronopathy Dorsal root ganglia Chronic gastrointestinal pseudo-obstruction Myenteric plexus Lambert–Eaton myasthenic syndrome Neuromuscular junction Dermatomyositis Muscle Table 24.23.2 Onconeural antibody-associated

paraneoplastic syndromes Antibody to Neuronal reactivity Cloned genes Tumour Clinical syndromes Hu Nucleus>cytoplasm (all neurones) HuD, HuC SCLC, neuroblastoma,, prostate PEM, PSN, PCD, gastrointestinal pseudo-obstruction Yo Cytoplasm, Purkinje cells CDR34, CDR62 Ovary, breast, PCD Ri Nucleus>cytoplasm (CNS neurones) Nova Breast, gynaecological cancer, lung, bladder Brainstem encephalitis, opsoclonus–myoclonus Tr Cytoplasm, Purkinje cells Not known Hodgkin's disease PCD VGCC Presynaptic neuromuscular junction P/Q-type VGCC SCLC LEMS, PCD VGKC-complex Presynaptic: neuromuscular junction and CNS neurones LGI1 (nonparaneoplastic) and CASPR2 (paraneoplastic) Thymoma, SCLC Neuromyotonia, antonomic, limbic encephalitis or combinations of these (Morvan's syndrome) Retinal Photoreceptor, ganglion cells Recoverin and others SCLC, melanoma, gynaecological CAR, MAR Amphiphysin Presynaptic Amphiphysin Breast, SCLC Stiff person syndrome, PEM, myelopathy, and myoclonus CV2 (CRMP5) Oligodendrocytes cytoplasm CRMP5 (POP66) SCLC, thymoma PEM, PCD, chorea, sensory neuropathy, myelopathy, gastrointestinal pseudo-obstruction Ma1 Neurones (subnucleus) Ma1 Lung, others Brainstem, PCD Ma2 Neurones (subnucleus) Ma2 Testis Limbic/brainstem encephalitis NMDAR Surface membrane of hippocampal and other neurones NR1 subunit Ovarian teratoma Limbic encephalitis with prominent neuropsychiatric features progressing to movement disorders, fall in consciousness and autonomic instability AMPA receptor Surface of hippocampal and other neurones GluR1/2 SCLC, breast, thymoma Limbic Encephalitis GABA(B) receptor Surface of hippocampal and other neurones GABA(B1) or GABA(B2) SCLC Limbic Encephalitis Glycine
receptor Inhibitory synapses on neurones GlyRα1 and others Thymoma, lymphomas Stiff Person Syndrome often with dysautonomia and brainstem involvement mGluR5 Neuronal cell surface Metabotropic glutamate receptor Hodgkins disease
(2 cases reported) Limbic encephalitis Ganglionic form
of nAChR Ganglionic synapses Ganglionic AChR SCLC, thymoma autoimmune dysautonomia AChR, acetylcholine receptor; CAR, cancer-associated retinopathy; CNS, central nervous system; PCD, paraneoplastic cerebellar degeneration; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channels; VGKC, voltage-gated potassium channels; CRMP5 (collapsin response mediator protein). For other abbreviations, see text.

section 24 Neurological disorders 6386 (e.g. voltage-gated calcium channels and N-methyl-D-aspartate (NMDA) receptors). Certain autoantibodies are associated with specific tumours but widely varying paraneoplastic syndromes. For example, the anti- Hu antibody (Fig. 24.23.1) is almost always associated with SCLC (occasionally neuroblastoma or prostate cancer), but may be found in several different clinical syndromes usually encompassed by the term 'encephalomyelitis'. The clinical abnormalities include limbic encephalitis, paraneoplastic cerebellar degeneration, brainstem en- cephalitis, sensory neuronopathy, and autonomic failure. Some or all of these clinical abnormalities may be found in the same patient. Not all patients with a classical syndrome and associated tumour have onconeural antibodies. Thus, the absence of positive detect- able antibodies should not be taken as evidence that the patient has a nonparaneoplastic form of disease. In some conditions, there are no identified antibodies. A good example is opsoclonus–myoclonus associated with neuroblastoma in children. This paraneoplastic disorder is probably immune-mediated. The failure to find a disease- or tumour-specific antibody does not mean that one is not present, only that current techniques have not identified it. As techniques improve, new antibodies are regularly being reported; of particular interest is the discovery of antibodies directed against N-methyl-D-aspartate receptors (NMDAR) on hippocampal neur- ones in young female patients and children with a progressive en- cephalitis, many of which are associated

with ovarian teratomas (see ‘Further reading’). Tumours associated with PNS The most common tumours associated with PNS are found in lung (both SCLC and non-SCLC), ovary, breast, thymus, lymph nodes (both Hodgkin’s Disease and Non-Hodgkin’s Lymphoma) and testis. In a recent European survey, other tumours were also identified sug- gesting that whole-body scanning is appropriate in the diagnostic work-up of patients with suspected PNS. Diagnosis Certain clinical clues suggest that a neurological disorder may be a PNS. The onset is subacute or even acute; in some cases, the symptoms develop over a few days so that a stroke is initially sus- pected. Most PNS are progressive initially then stabilize after weeks to months, although more slowly progressive syndromes may occur. Recovery is rare in most of the central nervous system syn- dromes, probably because of irreversible neuronal loss and degen- eration, although improvement after oncological treatment have been reported. The neurological disorders are usually moderate or severe. Most patients have substantial disability by the time they first come to medical attention. Mild or waxing and waning neurological symptoms are rarely paraneoplastic. For example, the patient with paraneoplastic cerebellar degeneration is usually unable to walk or sit unsupported because of truncal ataxia, unable to write and, sometimes, unable to read because of oscillopsia. The neurological findings are often characteristic. A subacutely developing pancerebellar disorder, the rapid development of opsoclonus, or the development of LEMS strongly suggests cancer as the underlying cause. However, none of these syndromes, even the most characteristic, is invariably associated with cancer. Thus, only about two-thirds of patients with LEMS have cancer and only about 10% of patients with myasthenia gravis have a tumour (almost always thymoma). Probably about one-half of the patients with subacute cerebellar degeneration have cancer. Limbic enceph- alitis can present as both a paraneoplastic and a more common non- paraneoplastic form (Chapter 24.24). Imaging in suspected PNS is often normal or nonspecific. Indeed, one of the clues to the presence of a PNS is the relative normality of imaging in a patient with such severe clinical symptoms and signs. Occasionally MRI may show high signal within one or both medial temporal lobes (limbic encephalitis) or brainstem (brain- stem encephalitis), and very rarely diffuse oedema of the cerebellum (paraneoplastic cerebellar degeneration). The cerebrospinal fluid may show pleocytosis (30–40 cells), elevated protein, increased IgG, and oligoclonal bands, particularly early on in the course of disease, which then settles within a few weeks of onset. The immunoglobulin abnormalities usually persist. In a patient with a known cancer, the diagnosis of PNS should usually only be made after exclusion of the more common neurological complications of cancer, particularly malignant meningitis or treatment toxicity (e.g. chemotherapy- induced peripheral neuropathy). In a patient without a known cancer, particularly when con- ventional imaging studies (radiography, CT, ultrasonography, and mammography) are negative, the appropriate use of whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) may show a FDG-avid ‘hot spot’ suggestive of an occult malignancy (Fig. 24.23.2). Blood tumour markers are rarely helpful in this clin- ical context. If an onconeural antibody is present and the search for an underlying cancer is negative, the physician is obliged to follow 35–40 kDa Fig. 24.23.1 Anti-Hu antibodies: serum immunoreactivity with rat brainstem counterstained showing strong nuclear staining (solid arrow) and weaker cytoplasmic staining (dashed arrow) typical of anti-Hu (anti ANNA 1) antibodies (DAB-peroxidase counterstained with haematoxylin and eosin). Western blot shows a ‘ladder’ pattern of bands between 35 and 40 kDa. The patient was a woman with paraneoplastic cerebellar degeneration who was subsequently found to have lung cancer. Courtesy of Elizabeth Amyes Msc, University of Oxford.

24.23 Paraneoplastic neurological syndromes 6387 the patient carefully, searching periodically for a cancer. The recom- mended time for follow-up is five years from presentation, except for LEMS which is 18 months. The difficulties of defining and hence diagnosing PND have been carefully considered by an international panel of neurological ex- perts who have established guidelines for more rigorous diagnostic criteria. The aim of these guidelines has been to facilitate diagnosis, classification, and collaborative research. They rely on the defin- ition of ‘classical’ paraneoplastic syndromes and ‘well-characterized’ onconeural autoantibodies. On this basis a condition could be diag- nosed as paraneoplastic based on a descending hierarchy of fac- tors: (1) presence or absence of ‘classical’ syndrome; (2) presence or absence of cancer; (3) presence or absence of ‘well-characterized’ antineuronal antibodies and (4) exclusion of other possible causes of a similar neurological syndrome. On the basis of combinations of these criteria, the diagnosis of a PND is now either ‘definite’ or ‘possible’. (See ‘Further reading’.) Pathogenesis Current evidence suggests that PNS result from an autoimmune reaction to ‘onconeural’ antigens in the tumour. These antigens are those that are normally restricted to the nervous system (or the testis, which is also an immunologically privileged site). The immune system therefore recognizes the antigen as foreign and some patients mount an immune response. The immune response may have the beneficial effect of slowing tumour growth, but it can also damage those parts of the nervous system that express the antigen. Although many PNS are associated with specific neuronal autoantibodies, there is limited evidence that those directed against cytoplasmic or nuclear antigens are pathogenic. T lymphocytes recognizing these or other onconeural antigens, and other cellular immune mechan- isms, are the likely pathogenic agents in these conditions. In contrast, antibodies directed against membrane ion channels or receptors for neurotransmitters (e.g. voltage-gated calcium and potassium chan- nels, NMDA and AMPA forms of glutamate receptors) are patho- genic but are also often present in nonparaneoplastic forms of the disease. These antibodies recognize epitopes located at presynaptic or postsynaptic sites. Treatment Those PNS which are associated with antibodies to the neuronal surface proteins (NMDAR, AMPAR, GABA(B)R, CASPR2), such as LEMS, MG, and NMDAR encephalitis respond to immunosuppres- sion or to treatment of the underlying cancer (Table 24.23.3). Some syndromes, such as opsoclonus–myoclonus, may remit spontan- eously, but for most PNS associated with antibodies to intracellular Fig. 24.23.2 Axial T2W MRI brain of patient with limbic encephalitis showing high signal in left medial temporal lobe (arrow). Table 24.23.3 Treatable paraneoplastic neurological syndromes Syndrome Treatment Completely responsive Lambert–Eaton myasthenic syndrome (LEMS) Tumour therapy, plasma exchange, intravenous immunoglobulin, 3,4 diaminopyridine Myasthenia gravis Tumour therapy, plasma exchange, intravenous immunoglobulin, steroids, immunosuppressants, thymectomy, anticholinesterases Dermatomyositis Steroids, immunosuppressants, intravenous immunoglobulin Opsoclonus–myoclonus (children) Steroids, ACTH, tumour therapy Limbic encephalitis or other syndromes with antibodies to cell-surface antigens, e.g. VGKC, NMDAR, AMPAR, GABA(B)R, GlyR Tumour therapy, plasma exchange, intravenous immunoglobulin, immunosuppressants Neuromyotonia Antiepileptics, steroids, plasma exchange, tumour therapy Demyelinating neuropathy (osteosclerotic myeloma) Tumour therapy, radiation, bevacizumab Partially responsive Opsoclonus–myoclonus (adults) Steroids, tumour therapy, clonazepam, diazepam, baclofen Paraneoplastic cerebellar ataxia (Hodgkin’s disease) Tumour therapy Opsoclonus/ataxia (anti-Ri) Steroids, cyclophosphamide

section 24 Neurological disorders 6388 antigens, treatment is unrewarding, and the patient remains severely disabled even if the cancer is cured. Treatments usually involve im-

munosuppression with plasma exchange, intravenous immuno- globulin, steroids, or cytotoxic agents (e.g. cyclophosphamide), particularly for those syndromes associated with onconeural auto-antibodies. It is possible that the rapid onset of the syndromes does not allow sufficient time for accurate early diagnosis and for treat- ment to begin before irreversible neuronal damage has occurred. With earlier diagnosis, therapy may be more successful. However, as mentioned already, several of the ‘classical’ paraneoplastic con- ditions appear to exist in nonparaneoplastic forms (e.g. limbic en- cephalitis with potassium channel antibodies) and may respond to immunotherapies; therefore, if onconeural antibodies are absent, and no cancer is found, a trial of immunotherapy should be con- sidered. There has been interest in rituximab (anti-CD20 mono-clonal Ab) which has shown modest benefit in a small open trial of patients with PNS. Specific syndromes Brain and cranial nerves (See Box 24.23.1.) Paraneoplastic cerebellar degeneration Paraneoplastic cerebellar degeneration may complicate any ma- lignant tumour but is most common with lung cancer (especially SCLC), breast and gynaecological cancer, and Hodgkin’s disease. Males and females are both affected, and the age incidence reflects the age distribution of the underlying cancer. Neurological mani- festations precede detection of the associated tumour in over one- half of patients, rarely by more than five years, or paraneoplastic cerebellar degeneration may develop after diagnosis of the tumour. In some instances, the tumour is not found until autopsy. Typically, the disorder begins as gait ataxia that progresses over a few days to weeks to severe truncal and appendicular ataxia with dysarthria and nystagmus. The nystagmus is frequently downbeating. Vertigo with or without nausea and vomiting is common and many patients complain of diplopia. The cerebellar signs are bilateral but may be asymmetrical. The cerebellar deficit usually stabilizes but, by then, the patient is often incapacitated. Spontaneous improvement some- times occurs, particularly when associated with Hodgkin’s disease. Some patients will also be found to be mildly cognitively impaired and demonstrate extensor plantar reflexes or sensory changes sug- gesting a more widespread encephalomyelitis. The cerebrospinal fluid may be normal, but there is usually a pleocytosis within the first few months, and raised protein and oligoclonal bands may also be present. Cytological examination of the cerebrospinal fluid and contrast-enhanced MRI of the brain are essential to rule out leptomeningeal metastases. MRI scans typically are normal early, but later show signs of progressive cerebellar at- rophy with prominent cerebellar folia and a dilated fourth ventricle. The pathological hallmark of paraneoplastic cerebellar degener- ation is loss of Purkinje cells, affecting all parts of the cerebellum. Less striking changes in the cerebellar cortex may include thinning of the molecular layer with microglial proliferation and astrocytic gliosis, proliferation of Bergmann glia, and slight thinning of the granular layer with decreased numbers of granule cells. When typical, the clinical picture of paraneoplastic cerebellar degeneration is almost pathognomonic. When atypical, the dis-order must be distinguished from a cerebellar tumour (primary or metastatic) and from leptomeningeal metastases (by MRI and cerebrospinal fluid examination, respectively), from late-onset, nonparaneoplastic cerebellar degenerations, cerebellar haemor- rhage and infarction; prion diseases, cerebellar ataxia related to 5- fluorouracil, capecitabine or high-dose cytarabine, and metabolic disorders, especially alcoholic cerebellar degeneration. There have been occasional reports of a partial or near-complete remission of paraneoplastic cerebellar degeneration following treatment of the primary tumour. This is very unusual, however, and most patients do not improve even when treatment is begun early in the illness, before Purkinje cells are irreversibly dam- aged. Plasmapheresis, corticosteroids, immunosuppressive drugs, intravenous immunoglobulin, and rituximab have all been tried and may lead to mild symptomatic improvement in the ataxia. Paraneoplastic cerebellar degeneration may occasionally be as- sociated with LEMS, both

associated with SCLC and antivoltage- gated calcium channels antibodies. Recognition and treatment of the peripheral symptoms can lead to overall clinical benefits. In the future, nonparaneoplastic potentially treatable forms may be identified. Opsoclonus–myoclonus Opsoclonus is a disorder of eye movements consisting of almost continuous chaotic, multidirectional, involuntary, high-amplitude conjugate saccades that are often accompanied by synchronous blinking of the lids. It is usually considered to be a paraneoplastic syndrome complicating 2% of childhood neuroblastoma (dancing eyes syndrome) or a variety of tumours in adults, particularly breast cancer and SCLC, but there are cases that are nonparaneoplastic and self-limiting (see next). Opsoclonus may be an isolated neurological sign, but is often accompanied by myoclonus of the trunk, limbs, head, diaphragm, larynx, pharynx, and palate, and ataxia, hence the term opsoclonus– myoclonus or opsoclonus–myoclonus ataxia. Neurological symp- toms precede identification of the neuroblastoma in at least 50% of patients, and the tumour may be missed by abdominal examination; thus, recognition of the neurological syndrome is an important clue to the presence of a neuroblastoma. There are reports of antibodies to neuroblastoma cell lines but no specific antigen has been defined. When a neuroblastoma is associated with opsoclonus–myoclonus, there is a higher than expected incidence of intrathoracic tumours and of tumours with a benign histology. The prognosis of the neuro- blastoma is better if opsoclonus–myoclonus is associated than when there is no neurological complication, an observation not explained by earlier diagnosis when neurological symptoms are present. The neurological disorder responds to adrenocorticotropic hormone (ACTH) and to intravenous immunoglobulin but not to prednisone. Box 24.23.1 Paraneoplastic syndromes affecting the brain • Subacute cerebellar degeneration • Opsoclonus–myoclonus • Limbic encephalitis • Brainstem encephalitis

 However, most patients suffer residual neurological damage, usually cognitive. Opsoclonus–myoclonus is less common in adults, and in younger adults is often nonparaneoplastic. Nevertheless, about 20% of adult patients reported with opsoclonus–myoclonus have an underlying cancer. The neurological symptoms usually precede diagnosis of the tumour and commonly progress over several weeks, although more rapid or slower progression may be observed. The cerebrospinal fluid may show a mild pleocytosis and an elevated protein. The MRI is usually normal. Neuropathological findings have been variable. In some patients there are no identifiable abnormalities. In others, the changes resembled those of paraneoplastic cerebellar degeneration with a loss of Purkinje cells, inflammatory infiltrates in the brain- stem, Bergmann gliosis, and loss of cells from the granular layer of the cerebellum. The prognosis for recovery or partial remission of the neuro- logical disorder is better for opsoclonus–myoclonus than it is for paraneoplastic cerebellar degeneration. Improvement may follow treatment of the underlying tumour, and spontaneous partial re- missions occur. Differential diagnosis includes nonparaneoplastic conditions such as viral infections, postinfectious encephalitis, hydrocephalus, thalamic haemorrhage, and toxic encephalopathies from thallium or lithium, amitriptyline overdose, and diabetic hyperosmolar coma. Limbic encephalitis Limbic encephalitis may occur as an isolated finding initially, but the paraneoplastic forms frequently progress to a more extensive encephalomyelitis. The neurological symptoms often precede diag- nosis of the tumour by up to 2 years; sometimes the cancer is not detected until autopsy. Symptoms usually progress over several weeks, but the course may be more insidious. Anxiety and depres- sion are common early symptoms, but the most striking feature is a severe impairment of episodic memory. Other manifestations in- clude agitation, confusion, hallucinations, and partial or generalized seizures.

The symptoms may spread to include other brain func- tions (e.g. the hypothalamus), with changes in appetite or sleep (e.g. hypersomnia). Dementia usually occurs, but occasionally there may be a spontaneous remission; an increasing number of these cases are now known to be associated with antibodies to voltage-gated potas- sium channel complex proteins. Indeed, this test should now be sent off in any patient presenting with a rapidly progressive amnesic syn- drome, as it is treatable. The cerebrospinal fluid commonly shows a pleocytosis and an elevated protein concentration in PNS cases. MR scans are usually normal but medial temporal abnormalities have been reported (Fig. 24.23.3). Inflammatory pathological changes affect the grey matter of the hippocampus, cingulate gyrus, pyriform cortex, orbital surfaces of the frontal lobes, insula, and the amygdala. No treatment has proved uniformly beneficial although spontaneous remissions have been reported and some patients have improved after treatment of the underlying tumour. If onconeural antibodies are negative and there is no evidence of a tumour, immunosuppression should be con- sidered as recent studies have identified antibodies against novel cell-surface antigens (voltage-gated potassium channel complex proteins, LGI1, CASPR2, or NMDARs) which are associated with a favourable prognosis. NMDAR antibody encephalitis This condition, relatively recently described, has proved to be common, particularly in younger adults and children. Patients present with neuropsychiatric features, sometimes following a viral illness, and progress rapidly to a severe encephalop- athy with seizures, movement disorders, autonomic instability, and reduced consciousness. Despite the severity of the disease, the MRI is often normal or changes nonspecific, but the cere- brospinal fluid often shows pleocytosis during the first days. Oligoclonal bands tend to appear later. Ovarian teratomas or cysts are found in up to 50% of the adult females, but tumours are less common in males or the increasing number of children iden- tified, even within the first year of life. Removal of the ovary(s) and multiple symptomatic treatments are required, combined with immunotherapies with steroids, plasma exchange, and intravenous immunoglobulins; benefits may be evident within a few weeks but if not, rituximab and cyclophosphamide are recommended (see ‘Further reading’). Although many pa- tients require intensive care for weeks or months, the long-term prognosis is positive with a proportion returning to normal life particularly if identified and treated early. The ovarian tu- mours express NMDARs. Experimental results suggest that the antibodies reduce the number of hippocampal NMDARs in a reversible manner. Fig. 24.23.3 Whole-body FDG-PET scan showing two hot spots in right middle lobe (arrow) from patient with cerebellar degeneration and anti-Hu antibodies in whom chest radiography and CT of the thorax were both negative. Subsequent biopsy confirmed small-cell lung cancer.

section 24 Neurological disorders 6390 Brainstem encephalitis Paraneoplastic brainstem encephalitis is often associated with clin- ical and pathological evidence of encephalomyelitis elsewhere within the central and peripheral nervous systems, but may occur as the dominant or an isolated clinical finding. It is commonly associ- ated with SCLC, but an identical clinicopathological syndrome may be seen in the absence of a malignancy. The clinical features vary according to the brainstem structures involved in the pathological process. Common manifestations in- clude vertigo, ataxia, nystagmus, vomiting, bulbar palsy, oculomotor disorders, and corticospinal tract dysfunction. Less common clin- ical features include deafness, myoclonus of the palate, central al- veolar hypoventilation presenting with respiratory failure and jaw dystonia. Basal ganglia involvement produces movement disorders including chorea or Parkinson’s syndrome, these being more com- monly seen in patients with anti-CV2 antibodies. Neurological symptoms may develop before or after discovery of the malignancy. The pathological changes are identical to those ob- served in other forms of paraneoplastic encephalomyelitis. Visual loss PNS can affect retinal

photoreceptors, either rods or cones or both. They can cause a retinal vasculitis or optic neuropathy. Paraneoplastic retinal degeneration, also called cancer-associated retinopathy, usually occurs in association with SCLC, melanoma, and gynaecological tumours. Typically, the visual symptoms include episodic visual obscurations, night blindness, light-induced glare, photosensitivity, and impaired colour vision. Visual symptoms usually precede the diagnosis of cancer. The symptoms progress to painless visual loss. They may begin unilaterally but usually become bilateral. Visual testing demonstrates peripheral and ring scotomas and loss of acuity. Fundoscopic examination may reveal arteriolar narrowing and ab- normal mottling of the retinal pigment epithelium. The electroretino- gram is abnormal. Cerebrospinal fluid is typically normal, although elevated immunoglobulin levels have been reported. Inflammatory cells are sometimes seen in the vitreous by slit-lamp examination. Retinal antibodies (e.g. recoverin), although well recognized, are not routinely available in most countries. Pathologically, cancer-associated retinopathy is associated with a loss of photoreceptors and ganglion cells with inflammatory infiltrates and macrophages. The other parts of the optic pathway are preserved, although a loss of myelin and lymphocytic infiltration of the optic nerve may occur. Treatment of cancer-associated retinopathy is usually unsuc- cessful although a recent report describes improvement in some patients with the use of intravenous immunoglobulin. The condition is not recognized very frequently, and there may be nonparaneoplastic forms that are difficult to distinguish. Spinal cord and dorsal root ganglia (See Box 24.23.2.) Necrotizing myelopathy This is an extremely rare PNS. The initial symptoms of muscle weak- ness and sensory loss in the arms and legs may be asymmetrical, but eventually signs become bilateral and symmetrical. Back or ra- dicular pain may precede other neurological signs. Cerebrospinal fluid abnormalities may include an elevated level of protein and a mild pleocytosis. Swelling of the spinal cord may be apparent on MRI. Typically, the neurological deficit progresses rapidly over days or a few weeks, ultimately leading to respiratory failure and death. There is no effective treatment. Pathologically, there is widespread necrosis of the spinal cord, often most marked in the thoracic segments. The necrosis involves all components of the spinal cord with white matter usually more affected than grey matter. Motor neuron disease (amyotrophic lateral sclerosis) There is controversy as to whether motor neuron disease can be regarded as a classical PNS. It is likely to be paraneoplastic in three distinct groups of patients; the first with a rapidly progressive amyotrophic lateral sclerosis picture associated with anti-Hu antibodies; the second with primary lateral sclerosis and breast cancer; and the third with a subacute motor neuronopathy associated with lymphoma. Classical motor neuron disease in a patient with a pre- vious history of cancer is probably not paraneoplastic, merely re- flecting the occurrence of two reasonably common diseases of older age in the same patient separated in time. Myelitis Paraneoplastic myelitis is usually a part of the encephalomyelitis syndrome with inflammatory lesions elsewhere in the brain and dorsal root ganglia as well as the spinal cord. The clinical picture is dominated by the radicular element of a myeloradiculitis and is characterized by patchy wasting and weakness of muscles, some- times combined with fasciculations. The upper extremities are often more severely affected than the legs, reflecting predominant involve- ment of the cervical spinal cord. There may be striking weakness of neck and intercostal muscles, resulting in respiratory failure. Sensory symptoms and autonomic dysfunction may be present. Sensory neuronopathy Paraneoplastic sensory neuronopathy is most commonly asso- ciated with SCLC. Symptoms typically begin before the cancer is identified, with dysaesthetic pain and numbness in the legs or occa- sionally in the arm(s), face, or trunk. The symptoms may be asym- metrical at onset but progress over days to several weeks to involve the limbs, trunk, and sometimes the face, causing a severe sensory ataxia. All sensory modalities are affected. Deep tendon reflexes are lost

but motor function is preserved. Occasional patients have a mild and indolent neuropathy. The cerebrospinal fluid is typically inflammatory. Early pathological changes are limited mostly to the dorsal root ganglia, in which both a loss of neurones and the presence of lymphocytic inflammatory infiltrates are noted (Fig. 24.23.4). About 50% of patients with paraneoplastic sensory neuronopathy have pathological changes that may be clinically inapparent in other Box 24.23.2 Paraneoplastic syndromes affecting spinal cord and dorsal root ganglia • Sensory neuronopathy • Necrotizing myelopathy • Subacute motor neuronopathy • Motor neuron disease (primary lateral sclerosis) • Myelitis (as part of encephalomyelitis)

24.23 Paraneoplastic neurological syndromes 6391 regions of the nervous system. As with other PND, this disorder rarely responds to treatment. Peripheral nerves (See Box 24.23.3.) Sensory and sensorimotor neuropathy Peripheral neuropathies, particularly mild distal sensorimotor neuropathies, are common in patients with cancer and may be due to the metabolic or nutritional effects of late cancer, or associated with certain drugs (e.g. cisplatin). Some patients not known to have cancer, and who are not evi- dently systemically ill, present to the neurologist with a peripheral neuropathy that may be quite severe and disabling. It is estimated that about 10% of those patients whose initial evaluations do not reveal an obvious cause (such as vitamin B12 deficiency, alcohol, or diabetes), will eventually prove to have cancer as the underlying reason for the peripheral neuropathy. Paraneoplastic peripheral neuropathy may take several clinical and pathological forms. The most common is the distal, symmetrical, subacutely developing, sensory neuropathy which may be either axonal or demyelinating. A relatively pure sensory neuropathy, a mononeuritis multiplex due to microvasculitis, an acute polyradiculopathy, a focal neuropathy such as brachial neuritis, or an autonomic neuropathy may also be paraneoplastic. Most of these neuropathies are not associated with autoantibodies and the diagnosis is often one of exclusion. Neuromuscular junction and muscle (See Box 24.23.4.) Paraneoplastic disorders of the neuromuscular junction include the Lambert–Eaton myasthenic syndrome, myasthenia gravis, and acquired neuromyotonia. These disorders have a common patho- genetic mechanism—they are caused by antibodies against ion channels and, whether paraneoplastic or not, they respond to im- munological treatment. They are described in more detail in Chapter 24.18. Finally, because of its similarity to neuromyotonia, the stiff person syndrome is also included in this section. Whereas the more common nonparaneoplastic form is associated with antibodies to glutamic acid decarboxylase, the presence of amphiphysin or other onconeural antibodies should raise the suspicion of a tumour. Lambert–Eaton myasthenic syndrome Lambert–Eaton myasthenic syndrome (LEMS) results from a re- duced release of acetylcholine at presynaptic nerve terminals. The same P/Q-type voltage-gated calcium channels are found in small-cell lung cancers. Interestingly, the richest source of P/Q- type voltage-gated calcium channels is the cerebellum, perhaps explaining the occasional relationship of paraneoplastic cerebellar degeneration and LEMS. LEMS can be treated either by immune suppression or by treat- ment of the underlying cancer when present. Patients with SCLC associated with LEMS have a better prognosis than patients with SCLC who do not develop a paraneoplastic disorder, but this could be partly due to earlier diagnosis. Myasthenia gravis Myasthenia gravis occurs in 30% of patients with thymomas, and approximately 10% of patients with myasthenia gravis are found to have a thymoma. Usually the two are diagnosed synchronously but rarely myasthenia may develop many years after the thymoma, sometimes in association with other autoimmune diseases (e.g. red- cell aplasia). Polymyositis and dermatomyositis Only a minority of patients, usually older people, with polymyositis or dermatomyositis have an underlying malignancy as the cause. Dermatomyositis with typical

cutaneous changes is more likely to be paraneoplastic than polymyositis. Females and males are affected in approximately equal numbers. Symptoms of proximal muscle weak- ness, with pain and high creatine kinase levels, generally precede Fig. 24.23.4 Sensory ganglionitis: dorsal root ganglion with hypercellular nodules marking the site of ganglion cell degeneration. Another ganglion cell (dashed arrow) is in the process of degenerating. A healthy ganglion cell is shown in the bottom left-hand corner of the plate. Box 24.23.3 Paraneoplastic syndromes affecting peripheral nerves • Subacute or chronic sensorimotor peripheral neuropathy • Mononeuritis multiplex and microvasculitis of peripheral nerve • Brachial neuritis • Autonomic neuropathy (as part of anti-Hu syndrome) • Demyelinating peripheral neuropathy (myeloma or plasmacytoma) Box 24.23.4 Paraneoplastic syndromes affecting neuromuscular junction and muscle • Lambert–Eaton myasthenic syndrome • Myasthenia gravis • Dermatomyositis, polymyositis, acute necrotizing myopathy • Neuromyotonia

section 24 Neurological disorders 6392 identification of the cancer. The tumour may be at any site, but breast, lung, ovarian, and gastric malignancies are the most common. Corticosteroids, cyclosporin, and other immunosuppressants have been used successfully. Other reports suggest that high-dose intravenous immunoglobulin is useful in patients unresponsive to other forms of immunosuppression. Neuromyotonia and stiff person syndrome Muscle cramps are a common complication of cancer, sometimes re- lated to electrolyte imbalance or induced by chemotherapy. A much rarer but clinically significant PNS is acquired neuromyotonia. The disorder is characterized by muscle stiffness, cramps, and obvious rippling and twitching of muscles, sometimes leading to sustained abnormal postures. Relaxation after voluntary contraction is de- layed. Symptoms persist during sleep (and are abolished by curare). Sudden prolonged bursts of high-frequency, involuntary, repetitive muscle action potentials are seen on electromyography. The muscle spasms and rigidity are sometimes precipitated by activity, forcing patients to become sedentary. The disorder arises from peripheral nerves and is sometimes a part of the encephalo- myelitis syndrome. The disorder is usually nonparaneoplastic, but may be associated with cancer including thymomas and SCLC. Antibodies against voltage-gated potassium channels are often posi- tive (Chapter 24.24). Plasma exchange improves the patient’s condi- tion; but they often respond to anticonvulsants alone. Injection of IgG from affected patients into experimental animals can reproduce evidence of peripheral nerve hyperexcitability. Stiff person syndrome may superficially resemble neuromyotonia, but has a central origin and is usually not paraneoplastic. This rare disorder is clinically characterized by stiffness and rigidity, with epi- sodic spasms of axial muscles. A variant of the syndrome affects the limbs. Painful reflex spasms can occur in response to tactile stimuli or startle. Muscle action potentials are normal on electromyography but the activity is continuous and excessive and increased by volun- tary activity. The disorder is usually autoimmune, associated with antibodies against glutamic acid dehydroxylase; since this antibody is also important in type 1 diabetes, the assay is widely available. When paraneoplastic, it can be associated with lung or breast tu- mours, often with the appropriate onconeural antibody. Recently antibodies to glycine receptors have been recognized in patients with stiff person syndrome or a form of progressive encephalomy- elitis with rigidity and myoclonus. FURTHER READING Candler PM, et al. (2004). A follow up study of patients with paraneoplastic neurological disease in the United Kingdom. J Neurol Neurosurg Psychiatry, 75, 1411–15. Dalmau J, et al. (2011). Clinical experience and laboratory investi- gations in patients with anti-NMDAR encephalitis. Lancet Neurol, 10, 63–74. Giometto B, et al. (2010). Paraneoplastic neurologic syndromes in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol, 67, 330–35. Graus F, et al. (2004). Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg

Psychiatry, 75, 1135–40. Höftberger R, Rosenfeld MR, Dalmau J (2015). Update on neuro- logical paraneoplastic syndromes. Curr Opin Oncol, 27, 489–95. Kayser MS, et al. (2010). Psychiatric manifestations of paraneoplastic disorders. Am J Psychiatry, 167, 1039–50. Rees JH (2004). Paraneoplastic syndromes: when to suspect, how to confirm and how to manage. J Neurol Neurosurg Psychiatry, 75 Suppl 2, ii43–50. Vedeler CA, et al. (2006). Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. Eur J Neurol, 13, 682–90.

Revision #1
Created 2026-01-22 16:43:30 UTC by Omar Ayman
Updated 2026-01-22 16:43:30 UTC by Omar Ayman