# Paraneoplastic disorders of the nervous system

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## Introduction

Paraneoplastic neurologic disorders (PND) refer to an extensive group of syndromes that can affect any part of the nervous system by mechanisms that are mostly immune mediated (Table 1) [1]. PND are more frequent than previously considered, with an incidence that varies with tumour type. The tumours more frequently involved are small-cell lung cancer (SCLC, ~3% of patients develop PND), thymoma (15%), and the plasma cell dyscrasias associated with malignant monoclonal gammopathies (~5–15%). For solid tumours other than SCLC the incidence of PND is less than 1% [2].

In 60% of patients, symptoms of PND develop before the presence of a tumour is known; therefore, the majority of these patients are first seen by neurologists. In 40% of patients, symptoms of PND develop after the tumour diagnosis or at tumour recurrence. In this group of patients the diagnosis is also difficult because PND may mimic many neurologic complications of cancer or its treatment. In recent years the diagnosis of PND has been facilitated by serological tests that are based on the detection of antineuronal antibodies in the patients' serum or cerebrospinal fluid (CSF), but in at least 40% of patients no antibodies are detected, and in some instances the antibodies can be detected in cancer patients without PND [3]. Therefore, although testing for these antibodies is useful, it does not replace the importance of the clinical assessment that should always exclude other complications of cancer.

This review focuses on the general approach to the diagnosis and treatment of the most frequent immune-mediated PND, mainly those affecting the CNS.

## Pathogenesis

Many PND of the central nervous system (CNS) occur in association with immunological responses against intraneuronal antigens expressed by the underlying cancer (paraneoplastic or onconeuronal antigens). The

Table 1
Classification of immune mediated PND

| Area Involved | Classical Syndromes | Non-classical Syndromes |
|---|---|---|
| CNS | Encephalomyelitis<br>Limbic encephalitis<br>Cerebellar degeneration<br>Opsoclonus-myoclonus | Brainstem encephalitis<br>Stiff-person syndrome<br>Necrotising myelopathy<br>Motor neuron disease |
| Dorsal root ganglia or peripheral nerves | Subacute sensory neuronopathy<br>Gastrointestinal paresis or pseudo-obstruction | Acute sensorimotor neuropathy (Guillain-Barré syndrome, plexitis)<br>Subacute and chronic sensorimotor neuropathies<br>Neuropathy of plasma cell dyscrasias and lymphoma<br>Vasculitis of the nerve and muscle<br>Pure autonomic neuropathy<br>Acquired neuromyotonia |
| Muscle | Dermatomyositis | Acute necrotising myopathy<br>Polymyositis |
| Neuromuscular junction | LEMS | Myasthenia gravis |
| Eye and retina | Cancer-associated retinopathy<br>Melanoma-associated retinopathy | Optic neuritis |

Table 2
Non-metastatic neurologic complications of cancer different from immune mediated PND

| Syndrome | Proposed mechanism |
|---|---|
| Cerebrovascular disease | Coagulopathy |
| Wernicke-Korsakoff syndrome | Thiamine deficiency |
| Myelopathy, sensory neuropathy | Cobalamine (vitamin B12) deficiency |
| Pellagra-like syndrome | Niacin deficiency in carcinoid tumors |
| Diffuse metabolic encephalopathy | Hypoxia, organ failure, electrolyte imbalance, endocrine disorders |
| Opportunistic CNS infections | Cancer- or treatment-related immunodeficiency |
| POEMS neuropathy | Cytokines (IL-6, IL-1β, TNF-α), MMP, VEGF |
| Carcinoid myopathy | Increased serotonin secretion by carcinoid tumours |
| Cachectic myopathy | Proteolytic tumour-derived 'toxohormone'-like peptides, cytokines (TNF-α, IFN-γ, IL-6, IL-1β) |

IL: interleukin; TNF: tumour necrosis factor; MMP: matrix metalloproteinases; VEGF: vascular endothelial growth factor; IFN: interferon.

identification of infiltrates of T-cells in the patients' CNS, and the lack of success modelling the disease by transfer of antibodies have suggested that T-cells play an important role in the pathogenesis of these syndromes [4]. Studies show that in addition to paraneoplastic antibodies, T-cells specific for the paraneoplastic antigens are detectable in the patients' blood [5]. It is believed that after crossing the blood-brain barrier these T-cells are involved in the neuronal injury. It remains uncertain whether the T-cells are effective against the tumour, and if so, whether the anti-tumour effect is sustained enough to be clinically efficient [6]. Because many paraneoplastic antigens of PND of the CNS have been characterised, they are currently used in diagnostic tests that allow detection of paraneoplastic antibodies in patients' sera or CSF.

For many PND of the peripheral nerve and muscle the evidence of immune mediated mechanisms is also abundant but the target antigens are less well defined than in PND of the CNS. Evidence of immune mechanisms mainly relies on the detection of inflammatory infiltrates composed of T-cells. With a few exceptions (i.e. anti-Hu or anti-CV2/CRMP5) there are no surrogate antibody markers of the T-cell responses that can be used in clinical tests [7].

A direct pathogenic role of antibodies has been demonstrated in only a few disorders that can occur with or without a cancer association, such as myasthenia gravis and antibodies to the acetylcholine receptor (AChR) of the neuromuscular junction; Lambert–Eaton myasthenic syndrome (LEMS) and antibodies to P/Q type voltage-gated calcium channels (VGCC); neuromyotonia and antibodies to voltage-gated potassium channels (VGKC); and a subset of autonomic neuropathies and antibodies to the ganglionic AChR [8]. In contrast to PND of the CNS in which the antigens are usually intraneuronal, the antigens of antibody-mediated PND are receptors or ion channels expressed on the surface of nerves, or at the pre- or post-neuromuscular synapse.

In addition to the immune mediated PND, patients with cancer may develop neurologic dysfunction that results from a large and heterogeneous group of mechanisms unrelated to metastasis. These will not be further discussed but are listed in Table 2.

## General diagnostic approach

The diagnosis of PND is usually based on the recognition of the neurologic syndrome, the demonstration of the associated cancer, and the detection of serum and CSF paraneoplastic antibodies [3].

### *Recognition of the neurologic syndrome*

An extensive group of disorders similar to PND may occur in the absence of cancer (Table 3). However, some syndromes associate with cancer much more frequently than others, or the clinical features are characteristic enough that they readily suggest a paraneoplastic etiology. These syndromes are considered 'classical PND' (Table 1); two examples of these syndromes are LEMS and opsoclonus-myoclonus (OM).

Other syndromes may result from paraneoplastic mechanisms but occur more frequently in the absence of cancer. These syndromes are considered 'non-classical' and require a more extensive differential diagnosis. For example, chorea, motor neuron disease, or the Guillain–Barré syndrome may be paraneoplastic manifestations of cancer or lymphoma but are usually non-cancer related or their presentation in a patient with cancer may be merely coincidental.

Most PND develop and progress rapidly until stabilisation in a few weeks or months, causing severe

Table 3
Differential diagnosis of PND of the CNS

| PND | Differential Diagnosis | Additional considerations in patients known to have cancer |
|---|---|---|
| Cerebellar degeneration | Alcohol-related<br>Vitamin deficiency (B1, E)<br>Toxins (anticonvulsants, other)<br>Infectious or post-infectious cerebellitis<br>Miller–Fisher syndrome<br>GAD-associated ataxia<br>Gliadin-associated ataxia<br>Idiopathic | Cerebellar metastasis<br>Chemotherapy toxicity (5-FU, Ara-C) |
| Limbic encephalitis | Viral encephalitis (HSV)<br>Non-paraneoplastic (anti-VGKC)<br>Temporal lobe tumour<br>Systemic lupus erythematosus<br>Doxifluridine<br>Toxic-metabolic encephalopathy<br>Hashimoto's encephalitis<br>Sjögren's syndrome<br>Idiopathic | Brain metastasis<br>HHV 6 (in immunosuppressed patients) |
| Sensory neuronopathy | Sjögren's syndrome<br>Toxins (pyridoxine)<br>Idiopathic | Chemotherapy (cisplatin, paclitaxel, docetaxel, vincristine) |
| Opsoclonus-myoclonus | Infectious, post-infectious encephalitis<br>Metabolic encephalopathy<br>Toxins<br>Idiopathic | Brain metastasis |

5-FU: 5-fluorouracil; Ara-C: cytosine arabinoside; GAD: glutamic-acid decarboxylase; HSV: herpes simplex virus; HHV: human herpesvirus.

disability. Patients often become wheelchair bound or bedridden over a short period of time. PND that affect the CNS, dorsal-root ganglia or proximal nerve roots often associate with CSF lymphocytic pleocytosis, elevated IgG index, oligoclonal bands, or intrathecal synthesis of paraneoplastic antibodies. In most instances, CSF studies are required to rule out other cancer complications, such as leptomeningeal metastasis [9].

All patients with PND of the CNS and some peripheral nerve syndromes (i.e. plexopathies) should have neuroimaging evaluation of the involved area. MRI is the best technique to rule out metastatic lesions or other complications that may suggest a PND. In most PND of the CNS the function of the blood-brain-barrier is preserved and therefore, the affected brain regions rarely enhance with contrast. The abnormalities are usually demonstrated using T2 and fluid-attenuated inversion recovery (FLAIR) sequences. In syndromes such as limbic encephalitis with predominant hippocampal involvement (short-term memory loss, seizures) the MRI findings are often suggestive of the syndrome, although the etiology could be non-paraneoplastic [10].

*Associated cancer*

PND usually develop at early stages of cancer and therefore, the tumour (or tumour recurrence) may be difficult to demonstrate. Modern imaging techniques are able to demonstrate tumours whose size was often missed by the techniques used a few years ago. In most instances, the tumour is revealed by (CT) of the chest, abdomen and pelvis. The type of syndrome and paraneoplastic antibody may suggest a specific underlying tumour and the use of additional tests, such as mammogram or ultrasound of the pelvis or testes [11]. (18F)Fluorodeoxyglucose whole body positron emission tomography (FDG-PET) is very useful in demonstrating occult neoplasms or small metastatic lesions that may be more accessible for biopsy than the primary tumour (Fig. 1) [12]. False positive FDG-PET findings may occur and therefore the interpretation of the findings should be complemented with clinical information and paraneoplastic antibody testing.

In addition to radiologic or metabolic imaging, serum cancer markers such as carcinoembryonic antigen, Ca-125, CA-15.3, or prostate-specific antigen are helpful. All patients with a neuropathy of unclear

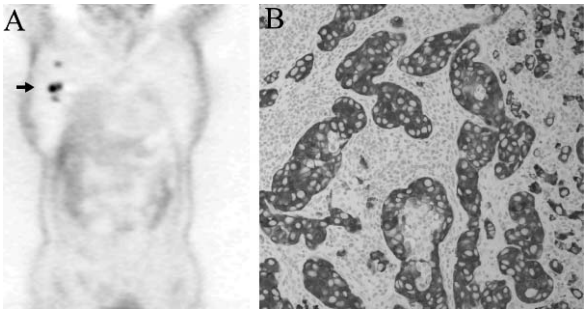


Fig. 1. Demonstration of a cancer in a patient with paraneoplastic cerebellar degeneration and anti-Yo antibodies. (A) PET scan demonstrating FDG uptake by several axillary lymph nodes (arrow); other studies including mammography had been negative. (B) Immunohistochemical analysis of a lymph node demonstrating neoplastic cells expressing the paraneoplastic Yo antigen (dark cells); the same cells were Her/2Neu positive (not shown). Immunoperoxidase technique ×400; background countertained with haematoxylin.

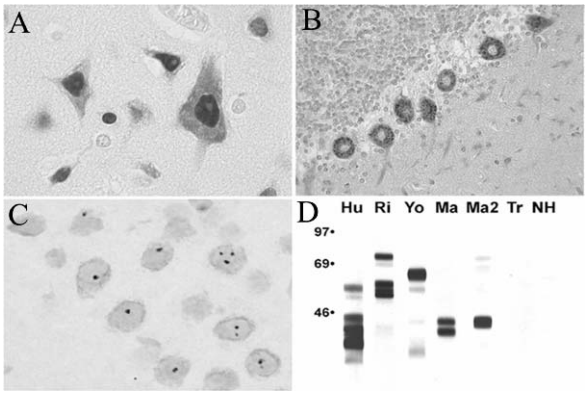


Fig. 2. Paraneoplastic antibodies. (A) Demonstration of anti-Hu antibody in a section of rat brain. The section was incubated with serum of a patient suspected ho have a paraneoplastic sensory neuronopathy. Note the intense reactivity of the antibodies (dark staining) with the nuclei of neurons (sparing the nucleoli). This finding combined with immunoblot studies confirmed the presence of the anti-Hu antibody, and focused the search of the tumour to the lung and mediastinum. The patient was found to have a small-cell lung cancer. (B) Demonstration of the anti-Yo antibody (using the same technique as in (A)) in a patient with a paraneoplastic syndrome. Note that this antibody predominantly reacts with Purkinje cells of the cerebellum and associates with cerebellar degeneration; the underlying neoplasm is usually a breast or ovarian cancer. (C) Demonstration of anti-Ma2 antibody (using the same technique as in (A)) in a patient with paraneoplastic limbic encephalitis. The reactivity predominates with nuclear inclusions (dot like). In young men this antibody usually indicates the presence of a germ-cell tumour in the testis. In older men and women other tumours are involved, mainly non-small-cell lung cancer. (D) Demonstration of paraneoplastic antibodies using immunoblot of normal neuronal proteins. A-C, immunoperoxidase technique A ×800, B-C ×400; background counterstained with haematoxylin.

etiology should be examined for the presence of a monoclonal gammopathy in the serum and urine, and if positive undergo a skeletal survey and bone marrow biopsy. These studies may uncover a malignant plasma cell dyscrasia, amyloidosis, or B-cell lymphoma [2].

Close oncologic surveillance should be undertaken in patients with classical PND with or without paraneoplastic antibodies, and patients with non-classical PND and paraneoplastic antibodies. A common practice is periodic cancer screening for at least 5 years [13]; in 90% of patients the underlying tumour is discovered within the first year of PND symptom presentation. Patients whose cancer is in remission and develop PND should be examined for tumour recurrence.

### *Paraneoplastic antibodies*

The term ‘paraneoplastic antibodies’ is applied to antibodies whose presence serves as a marker of the paraneoplastic origin of a neurologic syndrome (Fig. 2). Several concepts are important when testing for paraneoplastic antibodies (Table 4). First, antibodies are present in approximately 60% of patients with PND of the CNS; therefore, the absence of antibodies does not rule out that a syndrome could be paraneoplastic. Second, paraneoplastic antibodies may be identified (usually at low titer) in the serum of a variable proportion of patients with cancer but without PND (i.e. anti-Hu and anti-CV2/CRMP5 in 20% and 10% of patients with SCLC, respectively) [14,15]. Third, in PND of the CNS the antibodies are found in serum and CSF; detection of CSF antibodies is a strong indicator that the associated neurologic syndrome is paraneoplastic. Fourth, most PND of the peripheral nerve or muscle do not associate with paraneoplastic antibodies, except for anti-Hu and anti-CV2/CRMP5 antibodies. Fifth, not all paraneoplastic antibodies have the same sensitivity and specificity; based on their clinical relevance the paraneoplastic antibodies are classified in two categories: ‘well-characterised paraneoplastic antibodies’ and ‘partially-characterised antibodies’ [3] (Table 4).

Well-characterised paraneoplastic antibodies include: anti-Hu, Yo, Ma2, Ri, CV2/CRMP5, amphiphysin, and N-methyl-d-aspartate receptor (NMDAR). These antibodies and the corresponding antigens have been characterised by different laboratories or reported in large series of patients with PND. Detection of any of these antibodies strongly supports the diagnosis of PND even if no tumour is found at initial evaluation. Some antibodies are more syndrome specific than others; for example, anti-Yo antibodies almost always associate with cerebellar degeneration, and anti-Ma2 with limbic or upper brainstem dysfunction, while

Table 4
Paraneoplastic antibodies

| Antibody | Associated syndrome | Most frequent cancers |
|---|---|---|
| **Well characterised paraneoplastic antibodies** | | |
| Hu (ANNA1) | PEM, PSN, PCD, limbic encephalitis | SCLC |
| Yo (PCA1) | PCD | Ovary, breast |
| CV2/CRMP5 | Several | SCLC |
| Ri (ANNA2) | Ataxia, OM, brainstem encephalitis | Breast, gynaecologic, SCLC |
| Ma2[a] | Limbic, diencephalic, brainstem encephalitis | Testicular, lung |
| Amphiphysin | Stiff person syndrome, PEM | Breast, SCLC |
| NMDAR (NR1/NR2) | Encephalitis | Teratoma of the ovary or mediastinum |
| **Partially characterised paraneoplastic antibodies** | | |
| Tr | PCD | Hodgkin's disease |
| Zic4 | PCD | SCLC |
| PCA2 | Several | SCLC |
| ANNA3 | Several | SCLC |

[a] Some patients harbour Ma1 and Ma2 antibodies; the presence of Ma1 usually associates with predominant brainstem, cerebellar involvement, and tumours other than testicular neoplasms. The prognosis in patients with tumours other than testicular neoplasms is poorer than that of patients with Ma2 antibodies and testicular neoplasms.

Table 5
Antibodies that associate with the paraneoplastic and non-paraneoplastic forms of the neurologic disorder

| Antibody | Syndrome |
|---|---|
| AChR (nicotinic, neuromuscular junction) | MG |
| AChR (ganglionic or neuronal) | Autonomic neuropathy |
| P/Q VGCC[a] | LEMS |
| VGKC | Neuromyotonia, limbic encephalitis, Morvan's syndrome |

[a] In patients with cerebellar degeneration, with or without associated LEMS, detection of these antibodies should prompt the search of a SCLC.

anti-Hu or anti-CV2/CRMP5 antibodies associate with a much wider spectrum of symptoms.

As the name implies, 'partially-characterised antibodies' are those for which limited clinical experience is available or the target antigens are unknown. Until there is a larger clinical experience, detection of any of these antibodies is of limited diagnostic value and the management of these patients should be similar to those without paraneoplastic antibodies, including an extensive clinical, CSF and neuroimaging evaluation to rule out other more frequent complications of cancer.

Several antibodies, including P/Q type VGCC, VGKC, and nicotinic or ganglionic AChR antibodies can be detected in both the paraneoplastic and non-paraneoplastic form of the associated disorder (Table 5). These antibodies may assist in the diagnosis of the neurologic disorder, but do not predict the presence of a tumour. The same P/Q type VGCC antibodies that associate with the paraneoplastic and non-paraneoplastic forms of LEMS, have also been encountered in a subset of patients with PCD and SCLC; therefore, detection of these antibodies in patients with a subacute cerebellar syndrome should prompt the search for a SCLC [16].

## Diagnostic criteria of PND

The three sources of information discussed above (type of neurologic syndrome, detection of cancer, and presence or absence of paraneoplastic antibodies) have been used to define general guidelines for the diagnosis of PND, with the caveat that the diagnosis of the tumour and the development of the neurologic syndrome should both occur within 5 years [3] (Table 6). However, the use of body CT and FDG-PET allow detection of the tumour at the time of neurologic

Table 6
Diagnostic criteria for PND (adapted from[3])

| |
|---|
| **Definite PND** |
| A classical syndrome and cancer. |
| A non-classical syndrome that resolves or significantly improves after cancer treatment. |
| A non-classical syndrome with paraneoplastic antibodies (well-characterised or not) and cancer. |
| A neurologic syndrome (classical or not) with well-characterised antibodies, and no detected cancer. |
| **Possible PND** |
| A classical syndrome, no paraneoplastic antibodies and no cancer, but at high risk to have an underlying tumour. |
| A neurologic syndrome (classical or not) with partially characterised paraneoplastic antibodies and no detected cancer. |
| A non-classical syndrome with cancer, but without paraneoplastic antibodies. |

syndrome presentation in 80–90% of the patients. The indicated guidelines are useful but not perfect, and patients with criteria of 'possible PND' should be carefully considered for alternative diagnoses.

## Frequent paraneoplastic neurologic syndromes

### *Paraneoplastic encephalomyelitis (PEM)*

PEM refers to an immune mediated inflammatory disorder that can affect any part of the CNS, dorsal root ganglia, and autonomic nerves. The main areas involved include the hippocampus (limbic encephalitis), the Purkinje cells of the cerebellum (cerebellar degeneration), the lower brainstem (brainstem encephalitis), dorsal root ganglia (sensory neuronopathy), spinal cord (myelitis), and the sympathetic or parasympathetic ganglia and nerves (orthostatic hypotension, gastrointestinal paresis or pseudo-obstruction, cardiac arrhythmia, erectile dysfunction, abnormal pupillary responses to light) [17,18]. Less frequently, patients may develop discrete focal cortical encephalitis, sometimes presenting as epilepsia partialis continua. The diagnosis of PEM should be considered when the dominant symptoms result from involvement of two or more of the indicated areas.

Symptoms of PEM develop rapidly and progress over weeks or months until stabilisation or death. The CSF is almost always abnormal with mild to moderate lymphocytic pleocytosis, increased protein concentration, normal glucose concentration, and oligoclonal bands or increased IgG index [19]. Brain MRI is often abnormal, showing FLAIR or T2 sequences hyperintensities in involved areas and sometimes clinically silent regions; the abnormalities usually do not enhance after contrast administration. For reasons that are unclear, contrast enhancement is more likely to occur in some forms of encephalitis (i.e. limbic-diencephalic encephalitis associated with anti-Ma2 antibodies) than others (i.e. limbic encephalitis associated with anti-Hu antibodies) [20,21].

Several antibodies assist in the diagnosis of PEM and the underlying neoplasm (Table 4). The management of PEM is based on prompt treatment of the tumour along with immunosuppression. Although the standard of care remains to be established, the use of corticosteroids and intravenous immunoglobulin (IVIg) combined with chemotherapy may help to stabilise or improve the neurologic symptoms during the period of time that the tumour is treated. Afterwards, if the neurologic symptoms have stabilised or improved, patients should be considered for prolonged treatment with immunosuppressants that target not only the antibodies but also the T-cell immunity (i.e. cytoxan combined with corticosteroids, among other strategies) [6,22]. Patients with brainstem symptoms have a much poorer prognosis than patients with involvement of other areas of the CNS.

### *Limbic encephalitis*

Patients with limbic encephalitis develop short-term memory loss, seizures, confusion, irritability, depression, sleeping problems, or psychiatric symptoms [10]. The most characteristic clinical feature is dominant short-term memory loss, but the seizures, confusion or abnormal behaviour may limit the memory assessment. In patients with predominant short-term memory loss the MRI usually shows medial temporal lobe FLAIR or T2 abnormalities (Fig. 3); in other patients, the MRI shows more extensive abnormalities in the temporal lobes or beyond the limbic system. FDG-PET may show hyperactivity in regions that are normal in the MRI [20]. EEG often demonstrates uni- or bilateral temporal lobe epileptic discharges, or slow background activity. EEG monitoring is important in patients that appear confused or with low level of

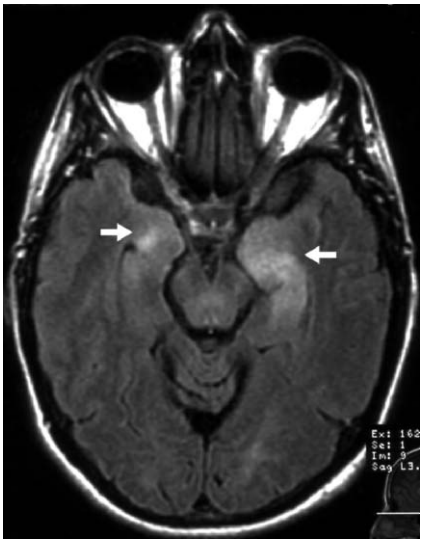

Fig. 3. MRI of a patient with limbic encephalitis. MRI fluid-attenuated inversion recovery (FLAIR) of a patient with paraneoplastic limbic encephalitis that caused severe short-term memory deficits and seizures. Note the characteristic increased signal in the medial temporal lobes (arrows).

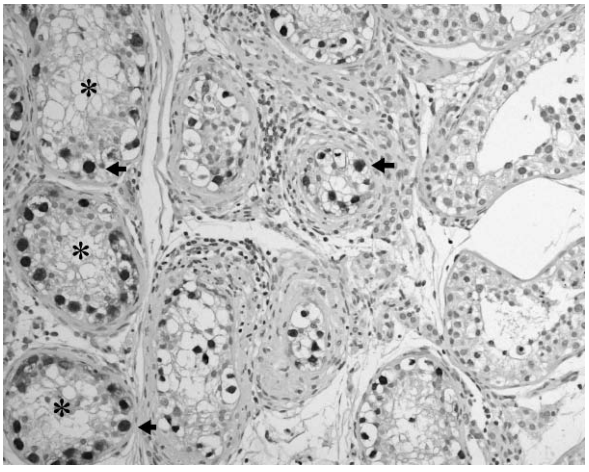

Fig. 4. Intratubular germ-cell neoplasm of the testis in a patient with paraneoplastic anti-Ma2 associated encephalitis. Oct4 immunostaining of a section of testis from a patient with subacute encephalitis, hypokinesis (parkinsonism-like symptoms) and paraneoplastic anti-Ma2 antibodies. Oct4 is a specific marker of seminomas and germ-cell tumours of the testis. Three seminiferous tubules with neoplastic (dark) cells lining the tubules are indicated with a ∗ in the lumen. Arrow demonstrates a neoplastic cell in another, smaller tubule. Immunoperoxidase technique ×400, background counternained with haematoxylin.

consciousness; many of them are in non-convulsive status epilepticus.

Antibodies usually found in paraneoplastic limbic encephalitis include, anti-Hu, anti-Ma2 and anti-CV2/CRMP5 [20,21,23]. Patients with anti-Hu or CV2/CRMP5 antibodies usually have SCLC. Detection of anti-Ma2 antibodies in young men usually associates with testicular neoplasms (Fig. 4); in elder men or women the leading neoplasm is non-SCLC.

The response of paraneoplastic limbic encephalitis to treatment is unpredictable; some patients show dramatic improvement if the tumour is treated promptly and, sometimes, with corticosteroids and IVIg, while others with similar symptoms and antibodies are refractory to treatment. Neurologic improvement is unlikely to occur if the tumour is not treated. There is some evidence that patients without paraneoplastic antibodies or young patients with anti-Ma2 antibodies are more likely to improve than patients with anti-Hu or CV2/CRMP5 antibodies [20,21].

Limbic encephalitis associated with VGKC antibodies has recently been described [24,25]. In this disorder, hyponatremia is frequent, and patients may also have accompanying autonomic and peripheral nerve dysfunction (neuromyotonia) and rapid eye movement sleep behaviour abnormalities [26]. The CSF of patients with limbic encephalitis and VGKC antibodies is usually normal or shows mild changes (elevation of proteins or oligoclonal bands; rarely pleocytosis) [27]. Although this disorder has been described as not paraneoplastic, in practice, patients should be examined for thymoma and lung cancer (particularly SCLC) because these tumours have been identified in some cases [28–30]. In 70–80% of patients with limbic encephalitis and VGKC antibodies, the use of corticosteroids, IVIg or plasma exchange result in significant improvement [13]. However, severe hyponatremia and non-convulsive status epilepticus can be life-threatening and should be aggressively treated (Dalmau, personal experience).

Recent studies suggest that several other antibodies to antigens predominantly expressed by the cell surface of neurons and dendritic processes of the hippocampus or cerebellum may associate with limbic encephalitis that frequently responds to treatment of the underlying tumour (teratoma, thymoma) and IgG-depleting strategies (plasma exchange, IVIg, and corticosteroids). Different from patients with VGKC antibodies, patients with these novel antibodies to cell surface antigens (initially called neuropil antibodies) usually have CSF abnormalities, including pleocytosis, increased protein concentration and elevated IgG index [31]. In some patients the antibodies are predominantly detected in the CSF, and the titres decrease as the syndrome resolves. Testing for these antibodies is not currently available in commercial laboratories, and their presence is usually missed with conventional immunohistochemical, immunoblot or immunoprecipitation techniques [27]. A study

examining the frequency of these novel antibodies suggested that they are more frequent than the VGKC antibodies [32].

*Encephalitis associated with ovarian teratoma*

A recently described group of patients develop subacute psychiatric symptoms, seizures, short-term memory deficits, decreased level of consciousness, autonomic dysfunction, and hypoventilation, usually requiring ventilatory support [33]. At symptom presentation, the psychiatric syndrome can dominate the clinical picture, including extreme agitation, delusional thinking, disorientation, and confusion that may progress to lethargy and stupor with the indicated ventilatory problems. Some patients develop prominent dyskinesias, choreic movements, dystonia, or catatonia [34]. The CSF usually shows pleocytosis, increased protein concentration and oligoclonal bands or elevated IgG index. Patients may require intensive care support for several weeks. An immature or mature ovarian teratoma (or 'dermoid cyst') is often found and can be overlooked if only FDG-PET is used for cancer detection. Resection of the tumour, corticosteroids, IVIg or plasma exchange often associates with improvement. In practice, these patients are first admitted to psychiatric wards, and the diagnoses of malingering and drug abuse are frequently considered. The serum (or sometimes only the CSF) contains antibodies that react with the NR1/NR2 heteromers of the NMDAR. Preliminary data strongly suggest that the antibodies are pathogenic. The disorder is important to recognise for two reasons, (1) experience suggests that it is more frequent than previously thought, (2) it is potentially lethal, but if recognised and treated, most patients recover. Patients who do not respond to the above indicated treatments often respond to cyclophosphamide [31].

*Paraneoplastic cerebellar degeneration (PCD)*

Patients with PCD usually present with dizziness, vertigo, oscillopsia, gait unsteadiness that in a few days or weeks evolves to frank gait and limb ataxia. Other clinical features include dysarthria, dysphagia, diplopia (often without obvious oculoparesis), and predominant downbeating nystagmus. The CSF usually shows the abnormalities common to most paraneoplastic syndromes of the CNS. MRI of the brain is usually normal at symptom presentation, and shows progressive cerebellar atrophy as the disease evolves [35].

The cerebellum is a common target of most paraneoplastic immunities (Fig. 5). Therefore, cerebellar

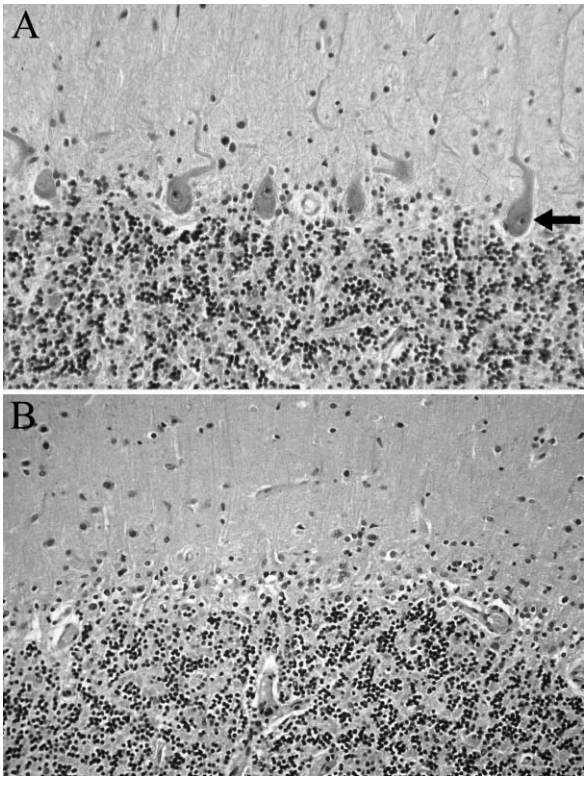


Fig. 5. Loss of Purkinje cells in paraneoplastic cerebellar degeneration. Section of cerebellum obtained at autopsy of a neurologically normal individual (A), and from a patient with paraneoplastic cerebellar degeneration (B). Arrow in (A) indicates a normal Purkinje cell. Note the absence of Purkinje cells in B. Haematoxylin-eosin, ×200.

symptoms may occur in association with any of the paraneoplastic antibodies shown in Table 4. The tumours more frequently associated with PCD are lung, ovary, breast cancer and lymphoma. A few antibodies (anti-Yo, anti-Tr) associate with dominant cerebellar symptoms without significant involvement of other areas of the nervous system [36,37]. Other antibodies usually associate with additional neurologic symptoms. Patients with PCD and SCLC should be evaluated for motor weakness because some of these patients may have LEMS [35].

As occurs with other PND, 30–40% of patients with PCD do not harbour antineuronal antibodies. In these patients the differential diagnosis is extensive (Table 3). PCD is one of the most difficult syndromes to treat, but prompt diagnosis and treatment may stabilise the disorder or prevent further involvement of other areas of the nervous system.

*Opsoclonus-myoclonus (OM)*

Opsoclonus is a disorder of eye motility with involuntary, chaotic, conjugate saccades. It almost always

associates with myoclonus of the trunk and limbs, and sometimes with truncal or limb ataxia. Some patients develop symptoms of diffuse encephalopathy that may lead to stupor, coma and death. In adults the tumours more frequently involved are SCLC, gynaecological and breast cancers [38]. In children, OM is usually accompanied by hypotonia, irritability, behavioural change, refusal to walk or sit, sleep dysfunction, episodes of rage, and psychomotor retardation. The underlying tumour is a neuroblastoma [39].

MRI studies are usually normal, and the CSF is normal or shows lymphocytic pleocytosis, increased protein concentration or oligoclonal bands. The pathological substrate of OM has not been established; autopsy studies can be normal or show encephalitis in the brainstem or cerebellum.

Most patients with paraneoplastic OM do not have detectable paraneoplastic antibodies. An exception is the anti-Ri antibody that identifies a subgroup of patients with OM, ataxia, breast or gynaecological cancers, and less frequently SCLC [40]. Other antibodies (i.e. anti-Yo, anti-Ma2, anti-Hu) have been reported in a few patients with opsoclonus associated to cerebellar or brainstem encephalitis.

Paraneoplastic OM may respond to IgG-depleting strategies (IVIg or plasma exchange and corticosteroids) and treatment of the tumour; improvement is rare if the tumour is not treated. There is an idiopathic form of OM that tends to occur in younger patients and responds better to immunotherapy [38]. Children with paraneoplastic OM may respond to treatment of the tumour, prednisone, ACTH, plasma exchange, IVIg, or rituximab [41]. The use of trazodone improves the episodes of rage [42]. Residual symptoms are common and most children are left with psychomotor retardation and behavioural problems [43].

### *Stiff-person syndrome*

In about 80% of patients with stiff-person syndrome the disorder develops as a non-paraneoplastic phenomenon in association with diabetes, polyendocrinopathy, and antibodies to glutamic-acid decarboxylase (GAD). Neurologic symptoms include fluctuating rigidity of the axial musculature with superimposed spasms precipitated by emotional upset and auditory or somesthetic stimuli. Muscle stiffness primarily affects the lower trunk and legs, but it can extend to the arms. Electrophysiological studies show continuous activity of motor units in the stiffened muscles that improve after treatment with diazepam. The rigidity improves during sleep or general anesthesia [44].

A similar syndrome may occur as a paraneoplastic manifestation of cancer of the breast, lung, and less frequently Hodgkin's lymphoma. Paraneoplastic stiff-person syndrome associates with antibodies to amphiphysin, and rarely with antibodies to GAD [45].

Treatment of the tumour and the use of steroids are usually effective. IVIg is useful in patients with non-paraneoplastic stiff-person syndrome, and likely effective in the paraneoplastic form of the disorder.

### *Paraneoplastic sensory neuronopathy (PSN)*

PSN is characterised by progressive numbness and often painful dysesthesias involving the limbs, trunk, and less frequently the cranial nerves causing face numbness or sensorineural hearing loss. The symptom presentation is frequently asymmetric, associated with decreased or abolished reflexes, and relative preservation of strength. All types of sensation can be affected, but loss of propioception is often predominant. As a result, patients develop sensory ataxia and pseudoathetoid movements of the extremities (predominantly hands) demonstrated when the patient closes the eyes or is distracted during the examination [46]. PSN results from inflammatory involvement of the dorsal root ganglia, usually accompanied with dorsal nerve root inflammation (Fig. 6). For this reason, symptoms are often asymmetric and the CSF shows inflammatory abnormalities. PSN frequently associates with PEM, particularly in patients with SCLC. These patients almost always harbour anti-Hu antibodies [17].

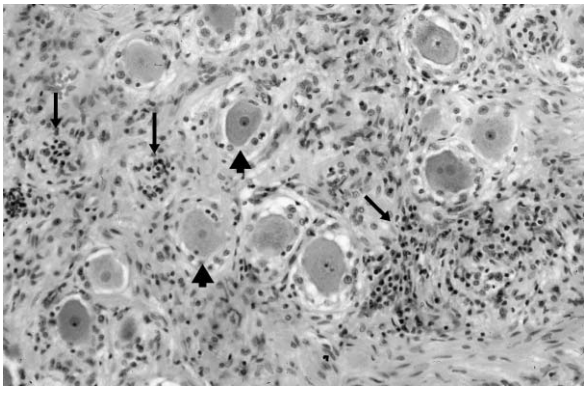

Fig. 6. Dorsal root ganglion from a patient with paraneoplastic sensory neuronopathy. Dorsal root ganglion from a patient with paraneoplastic anti-Hu associated sensory neuronopathy. Note the presence of extensive inflammatory infiltrates of mononuclear cells (mainly T-cells indicated with arrows). The large cells (thick arrows) are normal-appearing neurons. As a result of this immune mediated neuronal degeneration the patient developed severe, irreversible sensory deficits and ataxia. Haematoxylin-eosin $\times 200$.

Electrophysiological studies demonstrate that patients with dominant or isolated PSN have small-amplitude or absent sensory nerve action potentials with relative preservation of motor conduction velocities. Because PSN often overlaps with PEM, which may affect the lower motor neurons, and sometimes associates with peripheral neuropathy, the electrophysiological studies may show motor abnormalities [47, 48]. Autopsy studies indicate that when anti-Hu antibodies are detected in patients with sensorimotor neuropathies, the sensory component results from involvement of dorsal root ganglia and dorsal nerve roots [17]. Some of these patients harbour additional antibodies to CV2/CRMP5, which are also markers of PEM and some types of predominantly axonal peripheral neuropathies [7].

Prompt treatment of patients with corticosteroids and IVIg (along with treatment of the tumour) may result in stabilisation or mild improvement of the dorsal root ganglia dysfunction, sometimes confirmed with improvement of electrophysiological studies [49].

*Lambert–Eaton myasthenic syndrome (LEMS)*

LEMS results from an antibody-mediated attack against the P/Q type VGCC located at the presynaptic level of the neuromuscular junction. This interferes with the release of acethylcholine and results in muscle weakness and fatigability. LEMS should be suspected in patients with proximal weakness, dry mouth, and decreased or absent reflexes, particularly if the patient is known to have SCLC or a history of smoking [50]. In general, the legs are more involved than the arms. Mild muscle ache and distal paresthesias are common [51]. Cranial nerve involvement is frequent, but mild and transient, and almost always associated with motor weakness in the extremities. The symptom presentation of isolated ocular weakness virtually excludes the diagnosis of LEMS [52]. In addition to dry mouth, other signs of autonomic dysfunction may include orthostatic hypotension, erectile dysfunction and blurred vision due to abnormal pupillary responses. Electrophysiologic studies show small amplitude compound muscle action potentials. At slow rates of repetitive nerve stimulation (2–5 Hz) there is a decremental response, while at fast rates (20 Hz or greater) or after maximal voluntary muscle contraction, facilitation occurs with an incremental response of at least 100%.

Approximately 60% of patients with LEMS have an underlying neoplasm, usually SCLC or rarely other tumours such as lymphoma [50]. Paraneoplastic LEMS may associate with PCD or PEM [35]. The non-paraneoplastic cases often have a slower symptom presentation and associate with other autoimmune conditions such as thyroiditis, and insulin-dependant diabetes mellitus, among others [50]. Treatment of the tumour and medication that enhance acetylcholine release (3,4-diaminopyridine, or combination of pyridostigmine and guanidine) are usually effective [53]. IVIg and plasma exchange improve symptoms within 2–4 weeks but the benefit is transient. Long-term immunotherapy with prednisone or azathioprine is an alternative for patients who do not improve with 3,4-diaminopyridine [54].

*Polymyositis and dermatomyositis (PM/DM)*

PM/DM are inflammatory disorders of the muscle and are likely autoimmune in nature. The association of PM/DM with cancer is rare, and the existence of paraneoplastic PM controversial. However, a number of studies support the view that patients with DM are at higher risk for cancer [55–60]. In women the most common tumours are ovarian and breast cancer, and in men, lung and gastrointestinal cancer. An association with cancer has not been demonstrated in childhood DM.

Patients with PM/DM typically present with proximal muscle weakness of subacute onset, elevated levels of serum creatine kinase, and electromyographic evidence of myopathy. Neck flexors and pharyngeal and respiratory muscles are commonly involved; their dysfunction may result in aspiration and hypoventilation and contribute to death. Reflexes and sensory exam are normal.

In DM the classic skin manifestations include purplish discoloration of the eyelids (heliotrope rash) with oedema, and erythematous, scaly lesions over the knuckles. Necrotic skin ulcerations and pruritus are more frequently associated with paraneoplastic dermatomyositis [61].

Clinical, electromyographic, and pathological findings of PM/DM are similar in patients with and without cancer. In some patients, the serum creatine kinase levels are normal. Patients with interstitial lung disease may harbour antibodies to histidyl-tRNA synthetase (anti-Jo-1) [62]. There are no specific markers indicative of the paraneoplastic origin of DM.

Different immune mechanisms appear to be involved in PM and DM. While PM results from cell-mediated cytotoxic mechanisms, DM results from a humoral immuno-mediated vasculopathy leading to ischemia, muscle fibre necrosis, and perifascicular atrophy. Some patients develop cutaneous involvement

without myopathy (amyopathic dermatomyositis) in association with cancer; MRI studies may show subclinical muscle involvement [63].

Corticosteroids, IVIg, and other immunotherapies (azathioprine, cyclophosphamide, methotrexate, cyclosporine) have been used successfully in paraneoplastic and non-paraneoplastic PM/DM [64,65].

Patients with graft versus host disease (GVHD) may develop symptoms of PM. Some of these patients also have skin abnormalities secondary to GVHD which may resemble those associated with DM. Treatment with cyclosporine or tacrolimus in association with corticosteroids often results in improvement [66,67].

*Acute necrotising myopathy*

Patients with this disorder develop muscle pain and proximal weakness, associated with high levels of serum creatine kinase. The disorder evolves rapidly to generalised weakness, which involves pharyngeal and respiratory muscles, often leading to death in a few weeks. Several types of tumours are involved, including SCLC, cancer of the gastrointestinal tract (stomach, colon, gall bladder, pancreas), breast, kidney and prostate [68]. Muscle biopsy shows prominent necrosis with little or absent inflammation. There is alkaline phosphatase staining of connective tissue, and some muscle fibres are immunolabelled by antibodies to terminal components of the complement cascade (C5-C9). Treatment of the tumour may result in neurological improvement [68]. In cancer patients, the differential diagnosis should include chemotherapy and cytokine-induced (IL-2, interferon-α) rhabdomyolysis [69].

*Paraneoplastic visual syndromes*

Paraneoplastic retinopathy is characterised by progressive loss of photoreceptor function that usually precedes the diagnosis of cancer [70]. Symptoms include painless visual loss with night blindness, light-induced glare, photosensitivity, and peripheral and ring like scotomas. Funduscopic examination is normal or demonstrates arteriolar narrowing. The electroretinogram shows abnormal cone and rod-mediated responses. Paraneoplastic retinopathy associated with anti-recoverin antibodies is known as cancer-associated retinopathy (or CAR). Patients with anti-recoverin antibodies usually have SCLC [71].

Patients with metastasic melanoma may develop a paraneoplastic syndrome known as melanoma-associated retinopathy (MAR). Some patients with MAR have antibodies against bipolar cells of the retina.

The treatment of paraneoplastic retinopathies is based on controlling the tumour; there are a few reports of visual improvement after corticosteroids, IVIg, or plasma exchange, but the majority of patients do not improve with immunotherapy.

Optic neuritis is a rare paraneoplastic manifestation of cancer that may occur in association with other paraneoplastic syndromes of the CNS and several antibodies, mainly anti-CV2/CRMP5 and anti-Hu. The majority of these patients have SCLC.

## General treatment strategy for PND of the CNS

The treatment of PND is based on three concepts suggested by many studies: (1) a prompt diagnosis and treatment of the tumour is the main factor associated with stabilisation or improvement of PND and should be the main goal in the management of these disorders, (2) there is no evidence that immunosuppression favours tumour growth in PND patients, and (3) some patients benefit from immunosuppression.

*Paraneoplastic syndromes of the peripheral nervous system*

Most paraneoplastic syndromes of the peripheral nervous system have a counterpart that may present as a non-paraneoplastic syndrome. The neurologic symptoms of these paraneoplastic disorders should be treated similarly to those that occur as a non-paraneoplastic syndrome. For example, patients with paraneoplastic LEMS should be treated for the tumour and, in addition, with immunomodulation and immunosuppressants (Table 7) [72,74].

*Paraneoplastic syndromes of the central nervous system*

For PND of the CNS there is no standard of care. In general, when the autoantigen is intracellular (as occurs in most classical paraneoplastic syndromes, Hu, Yo, CV2/CRMP5 among others) the disorder appears to be mediated by cytotoxic T-cell responses [75]. A treatment strategy for these disorders (and disorders in which no antibodies are identified) is proposed in Table 8. Because the simultaneous use of chemotherapy and some immunosuppressants may result in significant toxicity, two levels of immunologic intervention are suggested. Patients with progressive PND who are receiving chemotherapy should be considered for immunosuppression or immunomodulation that may include oral or intravenous corticosteroids, IVIg, or plasma exchange. Patients with progressive PND, who are not receiving chemotherapy, should

Table 7
Paraneoplastic neuromuscular syndromes: Treatment approach (adapted from ref. [72])

| Disorders | Approach to therapy[a] |
|---|---|
| **Disorders that may Respond to therapy** | |
| Sensorimotor neuropathy | If demyelinating: PE, IVIg, immunosuppression |
| Sensory neuronopathy | Immunosuppression |
| Guillain–Barré | PE, IVIg |
| Neuropathy with monoclonal gammopathies: | Tumour<br>? PBSCT, IVIg |
| Osterosclerotic myeloma | Immunosuppression |
| POEMS | Rituximab, PBSCT, immunosuppression |
| Castleman's disease | PE, PBSCT |
| Waldenström's macroglubinemia | PE, IVIg, immunosuppression |
| MGUS with IgA, IgG<br>CIDP-MGUS<br>MGUS with IgM and MAG | Interferon-alpha, rituximab, immunosuppression |
| Vasculitis of nerve and muscle | Immunosuppression |
| Muscle rigidity, stiffness, spasms | PE, symptomatic[b] |
| Neuromyotonia<br>Stiff-man syndrome | IVIg, immunosuppression, symptomatic[c] |
| Inflammatory myopathies | Immunosuppression, ? IVIg |
| **Disorders that respond to therapy** | |
| Lambert–Eaton myasthenic syndrome | PE, IVIg, other[d] |
| Myasthenia gravis | PE, IVIg, other[e] |

PE – plasma exchange; IVIg – high-dose intravenous immunoglobulins; PBSCT – peripheral blood stem cell transplantation

[a] For all cases in which a tumour is identified, the approach always includes oncologic therapy. Immunosuppression may include one or a combination of agents and in reports of responses has included: corticosteroids, cyclophosphamide, azathioprine, fludarabine, chlorambucil

[b] Includes sodium channel blocking anti-epileptics

[c] Includes anxiolytics, anti-epileptic drugs, and centrally acting anti-spasticity agents. Other agents that have been reported as offering symptomatic relief in a few cases include dantrolene, botulinium toxin A, clonidine, and methocarbamol (reviewed in [73])

[d] Includes syndrome-specific treatments aimed at enhancing the release of acetylcholine: 3–4 diaminopyridine, guanidine and pyridostigmine and non-syndrome specific immunosuppressants: corticosteroids, azathioprine, cyclosporine

[e] Includes syndrome-specific treatments aimed at inhibiting acetylcholinesterase, i.e. pyridostigmine and non-syndrome specific immunosuppressants as listed for LEMS but also including mycophenolate mofetil.

be considered for more aggressive immunosuppression that may include oral or intravenous cyclophosphamide, tacrolimus, cyclosporine, or rituximab. Although there is no compelling evidence than any of these immunosuppressants is better than another, we and others favour the use of corticosteroids, IVIg and cyclophosphamide [22].

There is an emerging group of encephalitides that may present with predominant psychiatric dysfunction or as a clinical picture of limbic encephalopathy in association with antibodies to cell membrane antigens (in contrast with most classical paraneoplastic antigens that are intracellular). One of the autoantigens is the NMDAR, but there are other cell membrane antigens pending characterisation [27]. Despite the severity of the symptoms these disorders are usually responsive to removal of the tumour and corticosteroids, plasma exchange and IVIg [31,32].

## Conflict of interest statement

None declared.

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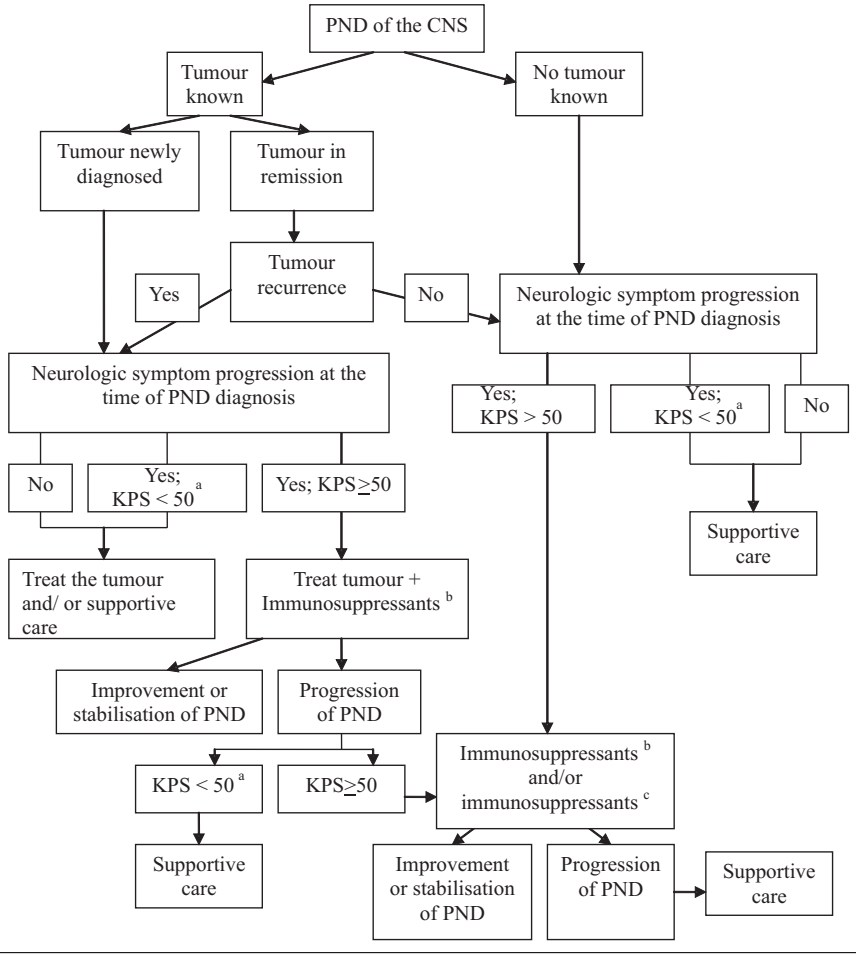
Table 8
Paraneoplastic syndromes of the CNS: Treatment approach (adapted from Dalmau, 2006 [76])




[a] Because patients with limbic encephalitis or opsoclonus/myoclonus may show dramatic improvement to immunosuppression, patients with these two disorders and KPS<50 may be considered for immunosuppression
[b] May include IVIg, and/or intravenous or oral steroids, and/or plasma exchange
[c] May include, cyclophosphamide and/or rituximab, or tacrolimus.
Variable efficacy (class 4–5 level of evidence) has been reported for IVIg, steroids, plasma exchange or protein-A IgG absorption, cyclophosphamide, and rituximab. Tacrolimus has been suggested as treatment; clinical studies are not available.
KPS: Karnofsky performance status.

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