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Paraneoplastic syndromes of the CNS

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Abstract

Major advances in the management of paraneoplastic neurologic disorders (PND) include the detection of new antineuronal antibodies, the improved characterisation of known syndromes, the discovery of new syndromes, and the use of CT and PET to reveal the associated tumours at an early stage. In addition, the definition of useful clinical criteria has facilitated the early recognition and treatment of these disorders. In this article, we review some classic concepts about PND and recent clinical and immunological developments, focusing on paraneoplastic cerebellar degeneration, opsoclonus-myoclonus, and encephalitides affecting the limbic system.

Introduction

In 1949, Guichard and Vignon¹ used the term paraneoplastic in a discussion of the differential diagnosis of a patient with multiple cranial and radicular neuropathies caused by metastases of a neoplasm of the uterus. Guichard and colleagues² subsequently studied three patients suspected of having similar metastatic neuropathies, the autopsies of whom did not reveal neoplastic cells in their spinal cords and nerve roots. These authors proposed that the term paraneoplastic was more appropriate than neoplastic to describe such polyneuropathies. The same term was later used to describe many complications that could not be attributed to identifiable mechanisms, such as direct invasion of the nervous system by the neoplasm, infections, coagulopathy, or side-effects of cancer treatment. Therefore, any symptom of unclear cause but associated with the presence of a neoplasm was considered paraneoplastic. Over the past 20 years, the discovery that many paraneoplastic neurological disorders (PND) are associated with antineuronal antibodies has resulted in tests that, along with recently defined clinical criteria, facilitate their diagnosis. Consequently, patients are diagnosed faster and treated earlier and more effectively than in the past. Patients whose symptoms do not conform to any of the classic PND or who do not have antineuronal antibodies have been studied further, resulting in the discovery of disorders that, in fact, are immune mediated and associated with new antibodies that are likely to be pathogenic.

In this Review, we focus on recent developments and new concepts in PND related to paraneoplastic cerebellar degeneration, opsoclonus-myoclonus, and encephalitides (table 1).³⁻⁵ Comprehensive reviews of PND of the peripheral nervous system have recently been reported in *The Lancet Neurology* and elsewhere;³⁻⁶ we do not address these disorders or those affecting the spinal cord and visual system in this Review.

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Contributors

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Conflicts of interest

We have no conflicts of interest.

Epidemiology

Some researchers suggest that about one per 10 000 patients with cancer develop PND,⁷ although there are no data to support such a low prevalence. A report based on serological screening of patients with suspected PND without further selection criteria showed that among 60 000 consecutive cases examined in 4 years, 553 (0.9%) were positive for antibodies associated with PND.⁸ By contrast, a review of patients examined in a research laboratory in which most samples are preselected by use of clinical criteria showed that among 649 cases consecutively examined in 23 months, 163 (25%) were serologically positive (Dalmau J, unpublished). Neither of these numbers shows the true prevalence of PND, but they do emphasise the importance of clinical criteria.

Tumours commonly involved in PND of the CNS express neuroendocrine proteins (eg, small-cell lung cancer, neuroblastoma), affect organs with immunoregulatory properties (thymoma), or contain mature or immature neuronal tissue (teratomas). Tumours that derive from cells that produce immunoglobulins (plasma-cell dyscrasias, B-cell lymphomas) are more commonly involved in PND of the peripheral nervous system than other tumour types.⁹ About 3–5% of patients with small-cell lung cancer,¹⁰ 15–20% with thymomas, and 3–10% with B-cell or plasma-cell neoplasms develop PND. The prevalence of PND in other neoplasms, including cancer of the breast or ovary and others cancers, is well below 1%.

Immune responses and pathogenic mechanisms

Most PND of the CNS are probably immune mediated, the best evidence for which comes from the demonstration of antineuronal antibodies in the CSF and serum of patients (table 2). These antibodies react with neuronal proteins that are usually expressed by the patients' tumour, and their detection is the basis of useful diagnostic tests.

Antibody-mediated PND

Some antibodies seem to have a direct pathogenic role in causing PND. These antibodies usually react with cell-surface antigens and until recently were thought to be mainly involved in syndromes of the neuromuscular junction or peripheral nerves. The associated symptoms and electrophysiological abnormalities of most of these immune responses have been modelled in animals. Antibodies to cell-surface antigens and the associated disorders can occur with or without cancer.¹¹ The relative risk of a paraneoplastic cause depends on the type of syndrome; for example, the likelihood of an underlying tumour is higher in the Lambert-Eaton myasthenic syndrome (50%, commonly small-cell lung cancer) than in myasthenia gravis (10%, typically thymoma).¹² Some patients with paraneoplastic cerebellar degeneration have antibodies against P/Q type voltage-gated calcium channels.¹³ Similarly, antibodies against voltage-gated potassium channels are associated not only with peripheral nerve hyperexcitability, but also with limbic encephalitis and Morvan's syndrome.^{14,15}

Antibodies against mGluR1 were identified in two patients who developed cerebellar ataxia after being in remission from Hodgkin's lymphoma for 2 years and 9 years. Passive transfer of these antibodies to the cerebellar subarachnoid space of mice caused severe, reversible ataxia.¹⁶ No other patients have been reported, suggesting that this disorder is uncommon. However, the description of antibodies to Homer 3, an mGluR1 C-terminus-interacting protein, in a patient with idiopathic cerebellar ataxia suggests that autoimmunity to synaptic metabotropic proteins results in cerebellar dysfunction.¹⁷

Antibodies to N-methyl-D-aspartate (NMDA) receptors seem to be associated with a severe form of encephalitis that usually presents with psychiatric symptoms and less commonly with

short-term memory deficits.¹⁸ These antibodies react with cell-surface epitopes that are present in NR1/NR2 heteromers of NMDA receptors and might be pathogenic.

Other disorders for which a humoral immuno-pathogenesis is strongly suggested include the cerebellar and stiff-person syndromes associated with antibodies against glutamic acid decarboxylase, and the paraneoplastic stiff-person syndrome related to antibodies against amphiphysin. Glutamic acid decarboxylase and amphiphysin are intracellular, close to the synaptic membrane, and antibodies against them seem to have a functional effect in vivo.^{19, 20} In the rat model that involved systemic passive transfer of patients' IgG-containing amphiphysin antibodies, the functional effects were observed after disruption of the blood–brain barrier with encephalitogenic T-helper lymphocytes specific for myelin basic protein.²⁰

T-cell-mediated PND

In contrast to the above disorders, other PND of the CNS seem to be mediated by T-cell immune responses that are probably directed against the target antigens of the accompanying antibodies. The best, but still circumstantial, evidence of T-cell-mediated pathogenesis comes from studies of patients with anti-Yo (also known as cdr2) or anti-Hu antibodies in whom cdr2-specific or Hu-specific T cells have been identified in the blood or CSF.^{21–23} However, some of the initial findings related to cdr2-specific T-cells in patients' blood have not been reproduced by other investigators using interferon- γ ELISPOT and highly sensitive immune-assessment assays.^{24,25} One study suggested that anti-Hu antibodies induced apoptosis when applied to cultures of neuroblastoma or myenteric cells.²⁶ However, all attempts to model the PND associated with these immune responses by passive transfer of antibodies or by protein or DNA immunisation failed to reproduce the symptoms.^{27–29} Adoptive transfer of T cells specific for autologous Ma1 in rats produced perivascular and meningeal lymphocytic infiltrates that were indistinguishable from those induced by CD4+ T cells against myelin proteins.³⁰ However, the rats did not develop symptoms or pathological features that characterise PND, such as predominant parenchymal inflammatory infiltrates in the hippocampi, brainstem, or diencephalon, neuronophagic nodules of T-cells, neuronal degeneration, and gliosis.³¹

Further support for T-cell-mediated mechanisms in some PND of the CNS comes from the following findings: difficulty in treating these disorders with strategies directed at the humoral immune response;^{32–34} the presence of extensive infiltrates of T cells in the CNS of patients;^{35,36} and the presence of oligoclonal cytotoxic T-cell infiltrates in the brains and tumours of patients with anti-Hu-associated encephalomyelitis, suggesting a specific antigen-driven clonal expansion of T cells.³⁷

Diagnosis of PND

The initial diagnostic approach in patients with suspected PND of the CNS (figure 1) is straightforward for patients with a classic syndrome in association with well characterised paraneoplastic antibodies or a demonstrable tumour (tables 1 and 2). However, not all patients have well characterised paraneoplastic antibodies, and other clinical scenarios are common, including patients with atypical syndromes or those whose tumour cannot be found. In such cases, a firm diagnosis of PND is difficult to establish even when a brain biopsy is done, as other disorders can have similar pathological signs. To resolve some of these issues, specific diagnostic criteria have been defined (panel).³⁸ Recent developments suggest that an expansion of these criteria is already needed.

Two clinical features shared by most PND of the CNS are the rapid development of symptoms and signs of inflammation in the CSF, including moderate lymphocytic pleocytosis, increased protein concentration, high IgG index, and CSF-specific oligoclonal bands. In about 70% of patients with PND, neurological symptoms are the first manifestation of a tumour.³⁹ Of these

patients, 70–80% will have a positive screening for cancer on initial assessment. Most tumours are identified with imaging of the chest, abdomen, and pelvis using CT, fluorodeoxyglucose-PET, or both.^{40,41} Some tumours of the gonads might require a different approach. For example, mature ovarian teratomas do not have uptake of fluorodeoxyglucose and are better shown with CT, MRI, or pelvic and transvaginal ultrasound. Microscopic intratubular germ-cell testicular neoplasms are not visible with any tests.⁴² However, the associated PND, age of the patients (usually younger than 50 years), and common development of testicular microcalcifications lead to further studies, such as repeat ultrasound, biopsy, or unilateral orchiectomy, that eventually reveal the tumour.

Panel: Diagnostic criteria of PND of the CNS³⁸

Definite PND

1. Classic syndrome with cancer diagnosed within 5 years of neurological symptom development
2. Non-classic syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission
3. Non-classic syndrome with cancer diagnosed within 5 years of neurological symptom development and positive neuronal antibodies
4. Neurological syndrome (classic or not) without cancer and with well characterised antineuronal antibodies (Hu, Yo, CV2/CRMP5, Ri, Ma2, or amphiphysin)

Possible PND

1. Classic syndrome with high risk of cancer, without antineuronal antibodies
2. Neurological syndrome (classic or not) without cancer and with partly characterised antineuronal antibodies
3. Non-classic syndrome with cancer diagnosed within 2 years of neurological symptom development, without neuronal antibodies

Paraneoplastic cerebellar degeneration

Cerebellar dysfunction is one of the most common paraneoplastic presentations of cancer. The tumours more commonly involved are small-cell lung cancer, gynaecological and breast tumours, and Hodgkin's lymphoma.^{34,43,44} Neurological deficits are sometimes preceded by prodromal symptoms, such as a viral-like illness, dizziness, nausea, or vomiting that might be attributed to a peripheral vestibular process.⁴⁵ These symptoms are followed by gait unsteadiness that rapidly develops into ataxia, diplopia, dysarthria, and dysphagia. Some patients have blurry vision, oscillopsia, and transient opsoclonus.^{44,46,47}

Initial MRI is normal in most patients, although some have transient diffuse cerebellar hemispheric enlargement or cortical-meningeal enhancement (figure 2).⁴⁸ During this early stage of the syndrome, fluorodeoxyglucose-PET can show cerebellar hyper-metabolism.⁴⁹ Over time, MRI shows cerebellar atrophy and PET demonstrates hypometabolism.

Common considerations in the differential diagnosis (table 3) are viral cerebellitis, Creutzfeldt-Jakob disease, and glutamic-acid-decarboxylase-associated cerebellar degeneration. Creutzfeldt-Jakob disease can mimic paraneoplastic cerebellar degeneration at onset; furthermore, 12.5% of patients with paraneoplastic syndromes of the CNS have 14-3-3 protein in the CSF, so this protein cannot distinguish the two disorders.⁵⁰ Compared with

paraneoplastic cerebellar degeneration, the syndrome associated with antibodies against glutamic acid decarboxylase has a slower progression, results in a milder and asymmetric limb ataxia (mainly affecting gait), is associated with polyendocrine dysfunction (late-onset insulin-dependant diabetes mellitus, thyroiditis, pernicious anaemia),⁵¹ and might present with transient or self-limited muscle spasms without developing into stiff-person syndrome.⁵²

The hallmark of paraneoplastic cerebellar degeneration is an extensive loss of Purkinje cells that might be associated with inflammatory infiltrates in the cerebellar cortex, deep cerebellar nuclei, and inferior olivary nuclei (figure 3). Patients with predominant cerebellar ataxia rarely die as a result of the neurological disorder; thus, neuropathological studies are uncommon and only those obtained at the early stage of the disease show inflammatory infiltrates.^{53,54}

An increasing number of immune responses are associated with paraneoplastic cerebellar degeneration (table 2). Some are specifically related to cerebellar symptoms, whereas others have no syndrome specificity and might simply reflect a tumour-induced immune response. Anti-Yo (cdr2), usually related to the presence of a gynaecological or breast cancer,^{44,55} and anti-Tr, often associated with Hodgkin's lymphoma,⁵⁶ are immune responses with high syndrome specificity.

Patients with small-cell lung cancer can develop one or multiple immune responses in association with paraneoplastic cerebellar degeneration.⁴³ In this setting, up to 41% of patients develop antibodies against voltage-gated calcium channels with or without associated Lambert-Eaton myasthenic syndrome, 23% develop anti-Hu antibodies, and a minority develops other antibodies, such as antibodies against collapsin-response mediator protein 5 (CRMP or CV2), amphiphysin, Purkinje cell cytoplasmic antibody type 2 (PCA2), and antineuronal nuclear antibody 3 (ANNA3).^{13,47,57,58} In contrast to the antibodies that target intracellular antigens, antibodies against voltage-gated calcium channels react with cell-surface epitopes; this and the fact that some patients have intrathecal synthesis of such antibodies has suggested a direct pathogenic role in the cerebellar dysfunction.

Recently described immune responses associated with cerebellar degeneration (table 4)⁵⁹⁻⁶⁹ have been found in only a few patients or in association with well characterised antibodies, but their clinical significance is unclear.

There is no standard of care for any of these syndromes. Clinical experience suggests that treatment of the tumour is needed for stabilisation or symptom improvement with or without immunotherapy. The use of corticosteroids, plasma exchange, intravenous immunoglobulin, cyclophosphamide, and tacrolimus did not substantially modify the neurological outcome of patients whose tumours were successfully treated.^{32,70,71} However, there are case reports of an apparent benefit from immunotherapy.^{72,73} The immune responses associated with more severe neurological deficits (Yo, Hu, CRMP5) are also the most refractory to treatment. Survival from time of diagnosis is significantly worse in patients with anti-Yo (median 13 months) or anti-Hu (median 7 months) than in patients with anti-Tr (median >113 months) or anti-Ri (median >69 months).³⁴ Patients who received antitumour treatment, with or without immunotherapy, lived significantly longer than those who did not.³⁴

The largest group of patients with paraneoplastic cerebellar degeneration without identifiable immune responses comprises those with non-small-cell lung cancer. In a study of nine patients, two had full neurological recovery and one had partial recovery after treatment of the tumour.⁶¹

Opsoclonus-myoclonus

Opsoclonus comprises involuntary, arrhythmic, chaotic, multi directional saccades with horizontal, vertical, and torsional components, and is commonly accompanied by myoclonic jerks in the limbs and trunk, cerebellar ataxia, tremor, and encephalopathy. Although the circuitry and exact physiopathological mechanism of opsoclonus remain unclear, findings of recent pathological⁷⁴ and functional MRI studies⁷⁵ suggest that disinhibition of the fastigial nucleus of the cerebellum is involved. The classic concept of damage of the omnipause cells in the nucleus raphe interpositus of the pons is not supported by autopsy studies.^{74,76}

Opsoclonus-myoclonus can occur with infections, toxic-metabolic disorders, and paraneoplastic mechanisms, among others (table 3).^{77,78} In children, the disorder is related to the presence of a neuroblastoma in about 50% of cases. In adults, the tumours most commonly involved include small-cell lung cancer and cancer of the breast and ovary. Although nearly all well characterised paraneoplastic antibodies have been reported in single case reports, most patients (both children and adults) are antibody negative. A small subset of adults, predominantly with breast and ovarian cancer, develops anti-Ri antibodies along with paraneoplastic brainstem and cerebellar dysfunction;⁷⁹ opsoclonus is common, but not always present in these patients.^{80,81} Several other antibodies have recently been identified (table 4).⁶³⁻⁶⁵

The most interesting immunological finding in opsoclonus-myoclonus is the progressive demonstration of antibodies against postsynaptic⁶⁵ or cell-surface antigens.^{82,83} Sera of children with opsoclonus-myoclonus have antibodies that react with the cell surfaces of cerebellar granular neurons and neuroblastoma cells;^{82,83} incubation of antibodies with neuroblastoma cell lines inhibits cell proliferation and induces apoptosis.⁸³ Overall, these findings suggest that humoral immune mechanisms have an important pathogenic role in opsoclonus-myoclonus and that there are multiple autoantigens.

In children with paraneoplastic opsoclonus, the immunotherapies used include corticosteroids, adrenocorticotrophic hormone, intravenous immunoglobulin, plasma exchange, cyclophosphamide, or rituximab.⁸⁴ Although opsoclonus commonly responds to treatment, the high frequency of residual motor, speech, behavioural, and sleep disorders is an important problem.⁸⁵ Trazodone improves the sleep and behavioural problems of some patients.⁸⁶ Symptom relapses can occur during intercurrent illnesses (eg, viral infections).

In adults, paraneoplastic opsoclonus-myoclonus is less responsive to immunotherapy. Corticosteroids or intravenous immunoglobulin might speed up improvement in patients with idiopathic opsoclonus, but not in those with paraneoplastic opsoclonus; the latter only responded when the tumour was controlled.⁸⁷ Immunotherapy seems to be helpful, but improvement is mild or not sustained unless the tumour is controlled.⁸⁸

Limbic encephalitis and variants

Limbic encephalitis is an inflammatory process highly confined to structures of the limbic system. Patients develop mood and sleep disturbances, seizures, hallucinations, and short-term memory loss that can progress to dementia.⁸⁹ Electroencephalography usually reveals foci of epileptic activity in one or both temporal lobes or focal or generalised slow activity.⁹⁰ In 70–80% of patients, MRI fluid-attenuated inversion recovery (FLAIR) or T2 sequences show hyperintense signals in the medial portion of one or both temporal lobes.^{89,90} Thus, in most patients with typical limbic encephalitis, the diagnosis is suggested by the clinical picture combined with findings on electroencephalography, MRI, and the indicated CSF inflammatory changes. Fluorodeoxyglucose-PET might show hypermetabolism in one or both temporal lobes that can precede the development of MRI changes or clinical symptoms (figure 4).⁹¹ When

seizures are excluded, hypermetabolism indicates the site of the inflammatory or immune-mediated process.⁹²

Both non-paraneoplastic (table 4) and paraneoplastic limbic encephalitis have similar clinical features. Identification of the paraneoplastic cause commonly depends on finding the tumour, the paraneoplastic antibodies, or both. The tumours more frequently involved are small-cell lung cancer, testicular germ-cell neoplasms, thymoma, Hodgkin's lymphoma, or teratoma.⁸⁹

Recent studies emphasise the importance of classifying limbic encephalitis into subphenotypes according to the location of the target antigens (table 5).^{14,18,47,92-97} Some patients who are negative for antibodies on standard testing have CSF inflammatory changes and improve with immunotherapy. Studies that have used other detection methods reveal that these patients have antibodies reacting with the neuropil of the hippocampus, cerebellum or both (figure 5).⁹² This pattern of neuropil staining is observed when the autoantigens are in the neuronal cell membrane.⁹⁸ By use of cultures of live neurons, the antigens exposed on the cell surface (eg, voltage-gated potassium channel, NMDA receptor) produce visible reactivity with patients' antibodies, whereas those that are on the cytoplasmic side of the cell membrane (eg, amphiphysin) or in the cytoplasm or nucleus (eg, GAD, Hu) do not react unless cells are permeabilised.

Limbic encephalitis with antibodies to intracellular antigens

The main intracellular antigens related to limbic encephalitis are Hu, Ma2, and less frequently CRMP5 and amphiphysin. In these immune responses, cytotoxic T-cell mechanisms are the main pathogenic effectors.

Anti-Hu—Many patients with these antibodies develop extensive or multifocal encephalomyelitis, which might be the end result of an initially focal syndrome, such as limbic encephalitis or cerebellar degeneration.^{93,99,100} Many patients who present with symptoms of pure limbic encephalitis have subtle signs of involvement of other areas of the nervous system and develop more widespread encephalitis.^{99,101} Most patients are smokers and the associated tumour is almost always a small-cell lung carcinoma. Only 50% of patients with these tumours and limbic encephalitis have anti-Hu antibodies; in such cases the prognosis is worse than in those without anti-Hu antibodies.¹⁰¹

Continuous partial epilepsy involving the extremities or tongue,¹⁰²⁻¹⁰⁴ orgasmic epilepsy,¹⁰⁵ and refractory complex partial status epilepticus¹⁰⁶ can be the presenting symptoms of anti-Hu-associated encephalitis involving the cerebral cortex, limbic system, or both. Prompt recognition of the disorder and treatment of the tumour can result in substantial and prolonged recovery.¹⁰⁵

Anti-CRMP5 (anti-CV2)—These antibodies are associated with encephalomyelitis, sensorimotor neuropathy, and more distinctively with cerebellar ataxia, chorea, uveitis, and optic neuritis.^{47,107,108} The development of myelitis and optic neuritis can resemble Devic's syndrome.¹⁰⁹ Thus, the clinical and MRI findings are rarely confined to the limbic system.¹¹⁰ In some patients, dysfunction of the frontostriatal and basal ganglia circuitry results in obsessive-compulsive behaviour and cognitive deficits.¹¹¹ Small-cell lung cancer and thymoma are the most common tumours involved.⁴⁷ In patients with small-cell lung cancer, CRMP5 antibodies might coexist with anti-Hu or Zic antibodies; these patients usually have multifocal deficits or encephalomyelitis.⁶⁰ Antibodies to other members of the CRMP family (CRMP3-4) were identified in a patient with limbic encephalitis, GAD antibodies, and thymoma.⁶⁷

Anti-Ma2—These antibodies are associated with encephalitis that characteristically affects the limbic system, hypothalamus, and brainstem.⁴⁶ The presenting symptoms can result from the involvement of any of these regions and can progress to involve the others. Therefore, in addition to limbic dysfunction, some patients present with excessive daytime sleepiness, narcolepsy, cataplexy, REM-sleep abnormalities, hyperphagia, decrease in CSF concentrations of hypocretin-1, and hypothalamic–pituitary hormonal deficits.^{94,112,113} Other patients present with severe hypokinesia and supranuclear gaze palsy that predominantly involves vertical gaze, and can develop to affect horizontal gaze and cranial nerve nuclei.¹¹⁴ Some patients develop orofacial and jaw dystonia that interfere with speech and eating; in one of our patients these symptoms were well controlled with local injections of botulinum toxin (Dalmau J, unpublished). At symptom presentation, CNS Whipple's disease is suspected in many patients. In one study, 16% of patients had duodenal biopsy before a paraneoplastic cause was investigated.¹¹⁵ Cerebellar dysfunction is rare, but patients with both Ma1 and Ma2 antibodies might have predominant cerebellar and brainstem dysfunction.⁹⁴ In a recent review of 62 patients, three had peripheral neuropathy.¹¹⁶ The small number of patients, including one with additional anti-Hu antibodies and small-cell lung cancer, and limited clinical information raise doubts about an association between anti-Ma immunity and peripheral neuropathy.

In men younger than the age of 50 years, anti-Ma2 encephalitis is almost always associated with testicular germ-cell tumours, which can be microscopic and difficult to demonstrate.⁴² Some authors suggest that the antibodies are part of an effective antitumour immune response that might explain the small size of the tumour.¹¹⁶ However, because germ-cell tumours (including those without paraneoplastic symptoms) can take several years to become clinically detectable, this association is probably due to the early detection of the tumour because of PND. In older men and women, the most common tumours are non-small-cell lung cancer and breast cancer.^{94,117}

Many patients with germ-cell tumours of the testes and anti-Ma2-associated encephalitis benefit from orchiectomy and immunotherapy that can include corticosteroids and intravenous immunoglobulin. Overall, 35% of patients with anti-Ma2 encephalitis have neurological responses to treatment.^{94,118} One case of spontaneous neurological improvement was recently reported.¹¹⁹

Other immune responses to intracellular antigens have been identified in a few patients with limbic encephalitis (table 4).⁶⁶⁻⁶⁹

Encephalitis with antibodies to neuronal cell-surface antigens

Antibodies against voltage-gated potassium channels—The two main CNS syndromes associated with these antibodies are typical limbic encephalitis and a less focal encephalitis that is associated with psychiatric symptoms, hallucinations, peripheral nerve hyperexcitability, hyper-hydrosis, and other symptoms of autonomic dysfunction (Morvan's syndrome).^{14,96} REM sleep disturbances and hyponatraemia are common in both,¹²⁰ and some patients develop hypothermia, hypersalivation, pain, and disorders of appetite.¹²¹ Symptoms of limbic encephalitis might be preferentially related to antibodies against the Kv1.1 subunit of the potassium channel whereas symptoms of neuromyotonia and Morvan's syndrome might be more closely related to antibodies to Kv1.2; standard clinical tests with immunoprecipitation assays do not differentiate between these subunits.¹²²

About 30% of patients with antibodies against voltage-gated potassium channels have tumours; but only 20% have tumours if small-cell lung cancers and thymomas are considered alone.⁹⁷ The neurological prognosis seems worse in patients with lung cancer and limbic encephalitis associated with these antibodies than in those without lung cancer.¹²³

Compared with other paraneoplastic or immune-mediated limbic encephalitis, the CSF of patients with antibodies against voltage-gated potassium channels shows less pleocytosis and lower protein concentration and intrathecal synthesis of IgG.^{92,124} Treatment comprises corticosteroids, plasma exchange, or intravenous immunoglobulin. About 80% of patients respond to these treatments. 6% of patients with long-standing epilepsy,¹²⁵ one patient with hyper-ekplexia,¹²⁶ and some people without neurological symptoms (Dalmau J, unpublished) have antibodies against these channels.

Antibodies against NMDA receptors—Most patients with this disorder are young women who, after prodromal symptoms that can include headache, fever, or a viral-like illness, develop severe psychiatric symptoms or memory loss, seizures, and decreased consciousness accompanied by dyskinesias,¹²⁷ hypo-ventilation, or autonomic instability.¹⁸ Symptoms commonly develop in sequence so that most patients are initially seen in or admitted to psychiatric centres and eventually transferred to intensive-care units. While unresponsive, patients are described to be in a catatonic-like stage, with limited eye contact or visual tracking, and paradoxical responses (eg, resisting eye opening while unresponsive to pain-inducing stimuli).^{128,129} Autonomic instability includes fluctuations of blood pressure, cardiac rhythm (from tachycardia to bradycardia or cardiac pauses), hyperthermia, and sialorrhea.

About 65% of patients have an underlying tumour, usually a cystic ovarian teratoma. The teratoma can be mature or immature, difficult to demonstrate, or, if found, difficult to remove because of the unstable clinical condition. Immunotherapy (corticosteroids, plasma exchange, intravenous immunoglobulin, rituximab, or cyclophosphamide) often results in improvement thereby enabling tumour removal.¹³⁰ Patients who do not respond to one form of immunotherapy might respond to another. Improvement can be slow and take several months. When a tumour is found, removal expedites recovery and decreases relapses. In a review of 69 patients, 65% had full or near-full recovery, and many returned to work. The disorder has recently been identified in children and a few men without tumour.¹³¹

Some patients previously described as having acute diffuse lymphocytic meningoencephalitis, juvenile acute non-herpetic encephalitis, or acute juvenile female non-herpetic encephalitis had anti-NMDA receptor encephalitis.¹²⁹ Owing to the profile of symptoms and orofacial dyskinesias, a few patients were initially suspected to have rabies.

Other immune responses to cell-membrane antigens—There are other antibodies to cell-surface antigens that have not been fully characterised (figure 5). Some of these antibodies occur along other well characterised immune responses, such as glutamic acid decarboxylase antibodies, and the associated disorders (eg, limbic encephalitis, muscle rigidity, and spasms) respond differently to immunotherapy.⁹² Whether these new antibodies have one or several target antigens is unclear. Tumours found in association with these antibodies include thymoma, small-cell lung cancer, and Hodgkin's lymphoma; similar antibodies might occur with non-paraneoplastic limbic encephalitis.⁹⁸

Antibodies against the subunit $\epsilon 2$ (or GluR $\epsilon 2$, also known as NR2B) of the NMDA receptor (not to be confused with antibodies against NR1/NR2 heteromers) have been reported in an extensive number of non-paraneoplastic syndromes, including Rasmussen's encephalitis, chronic epilepsy, limbic encephalitis, and stroke.^{132,133} These antibodies are detectable with immunoblotting of GluR $\epsilon 2$ (which differentiates them from antibodies against NR1/NR2) and have poor syndrome specificity. One patient with encephalitis and ovarian teratoma had GluR $\epsilon 2$ antibodies;⁶⁹ NR1/NR2 antibodies were not determined.

Additional considerations and future research

Progress in the study of PND is so rapid that recently defined clinical criteria already need expansion. For example, the discovery that SOX, a protein related to small-cell lung cancer, is the target of antibodies in 65% of patients with cancer-associated Lambert-Eaton myasthenic syndrome provides a potential test for differentiating paraneoplastic from non-paraneoplastic Lambert-Eaton myasthenic syndrome.¹³⁴ Anti-SOX antibodies seem to have the same predictive value of a paraneoplastic cause when detected in patients with limbic encephalitis and antibodies against voltage-gated potassium channels.¹³⁵ In addition, newly discovered disorders, such as the encephalitis associated with antibodies to NR1/NR2 heteromers of NMDA receptors, have been identified. Because the associated syndrome is highly predictable, it can now be added to the list of typical syndromes in the indicated criteria.³⁸

Treatment of PND of the CNS is challenging, particularly for disorders associated with antibodies to intracellular antigens that probably cause neuronal damage by cytotoxic-T-cell mechanisms. A review of several series of patients with these disorders emphasises the disappointing results of immuno therapy.^{34,93,99,100} However, these large series were gathered over many years, when the diagnoses of PND and associated tumours were delayed, unlike the early diagnoses that can now be made. Recent studies, and our experience, suggest that the combination of intravenous immunoglobulin or plasma exchange with cyclophosphamide might be effective in some cases.¹³⁶ The role of rituximab for these disorders is uncertain; in one study three of nine patients with anti-Hu or anti-Yo antibodies had some improvement, and a clinical trial is warranted.¹³⁷ The use of tacrolimus might downregulate cdr2-specific T cells in patients with cerebellar degeneration.²¹ Although limited information is available, one recently reported patient did not improve with tacrolimus,⁷¹ and in another the side-effects worsened the patient's already limited quality of life (Dalmau J, unpublished).

The small number of patients with PND that can be seen in a single institution makes it difficult to identify new syndromes. Nevertheless, the most relevant discoveries in PND stem from clinical observations of patients with similar symptoms whose serum and CSF were subsequently investigated. With this approach, the immune responses identified show a high degree of syndrome specificity and are therefore clinically relevant. Studies based on large-scale screening of sera or CSF with limited preselection clinical criteria rarely produce clinically relevant antibodies. New methods of antibody detection might be useful when standard results are negative. New approaches to detect antibodies to cell-surface antigens have revealed disorders that are indeed associated with antibodies. Similar studies should be pursued in patients with autoimmune opsoclonus and encephalitides, and expanded to other syndromes, because patients with these disorders are precisely those who are most likely to benefit from immunotherapy.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed from 1966 to December 2007 with the terms “paraneoplastic”, “cerebellar degeneration”, “encephalitis”, “limbic encephalitis”, “opsoclonus”, “cancer”, “antibodies”, “autoantigens”. Only papers published in English in peer-reviewed journals were selected. Articles were also identified through searches of the authors' own files.

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Figure 1. Initial diagnostic approach to PND of the CNS

*Well characterised onconeural antibodies. †Lymphocytic pleocytosis, high IgG index, and oligoclonal bands with or without high protein concentration.

Figure 2. Early MRI findings in paraneoplastic cerebellitis

Contrast enhancement in the sulci of the cerebellar vermis in a patient with non-Hodgkin's lymphoma and subacute cerebellar degeneration in association with anti-Tr antibodies. CSF showed pleocytosis, increased protein concentration, and high titres of anti-Tr antibodies, without malignant cells. Subsequent studies showed absence of contrast enhancement and progressive atrophy (not shown).

Figure 3. Inflammatory infiltrates in subacute cerebellar degeneration

CD3 T cells form clusters (A; arrows) at the level of the Purkinje cell layer. No remaining Purkinje cells are visible. Higher magnification (B) shows a neuronophagic nodule of T lymphocytes that are probably destroying a Purkinje cell. The patient had a subacute cerebellar syndrome in the context of encephalomyelitis and anti-Hu antibodies. A: $\times 100$, immunostained for CD3 and counterstained with haematoxylin. B: $\times 400$ haematoxylin-eosin.

Figure 4. Neuroimaging of patients with encephalitis

A and B: patient with anti-Hu-associated sensory neuronopathy. The patient was initially treated with intravenous immunoglobulin, corticosteroids, and oral cyclophosphamide, which resulted in symptom stabilisation. MRI of the brain (A) was normal. A body fluorodeoxyglucose-PET scan that included the brain revealed an area of hypermetabolism in the right hippocampus (B). The patient never developed symptoms of limbic encephalopathy. Small-cell lung cancer was eventually identified; the patient died as a result of tumour progression. C: typical increased FLAIR signal involving the hippocampi of a patient with paraneoplastic limbic encephalitis. D: medial temporal lobe FLAIR abnormalities and atrophy in a patient with a liver transplant who developed human herpes virus 6 (HHV6) encephalitis. The clinical picture and MRI findings of HHV6 closely mimic paraneoplastic limbic encephalitis.

Figure 5. Antibodies associated with paraneoplastic encephalitides

A and B: antibody reactivity in a rat brain with antibodies to NR1/NR2 heteromers of the NMDA receptor (A) and anti-Hu antibodies (B). Anti-NMDA receptor antibodies produce intense immunolabelling of the neuropil of the hippocampus whereas anti-Hu antibody staining is limited to neuronal cell bodies. C: cultures of non-permeabilised live neurons immunolabelled by antibodies contained in the CSF of a patient with anti-NMDA-receptor encephalitis. D: similar cultures immunolabelled with the CSF of a patient with limbic encephalitis and cancer of the thymus. The cell-surface antigen is unknown. Treatment of the tumour and intravenous immunoglobulin resulted in complete recovery. A and B: immunoperoxidase technique $\times 25$. C: immunofluorescence $\times 800$. D: immunofluorescence $\times 400$.

Table 1
Paraneoplastic syndromes of the nervous system by location

	Classic	Non-classic
Brain, cranial nerves, and retina	Cerebellar degeneration Limbic encephalitis Encephalomyelitis Opsoclonus-myoclonus	Brainstem encephalitis Optic neuritis Cancer-associated retinopathy Melanoma-associated retinopathy Stiff-person syndrome Myelitis Necrotising myelopathy Motor-neuron syndromes Myasthenia gravis
Spinal cord		
Neuromuscular junction*	Lambert-Eaton myasthenic syndrome	
Peripheral nerves or muscle*	Sensory neuropathy Intestinal pseudo-obstruction Dermatomyositis	Sensorimotor neuropathy Neuropathy and paraproteinaemia Neuropathy with vasculitis Acquired neuromyotonia Autonomic neuropathies Polymyositis Acute necrotising myopathy

* Disorder reviewed elsewhere.³⁻⁵

Table 2
Antibodies, paraneoplastic syndromes, and associated cancers

Syndrome	Associated cancers	
Well characterised paraneoplastic antibodies *		
Anti-Hu (ANNA-1)	PEM including cortical, limbic, brainstem encephalitis, PCD, myelitis, PSN, autonomic dysfunction	SCLC, other
Anti-Yo (PCA-1)	PCD	Gynaecological, breast
Anti-Ri (ANNA-2)	PCD, brainstem encephalitis, opsoclonus-myoclonus	Breast, gynaecological, SCLC
Anti-CV2/CRMP5	PEM, PCD, chorea, uveitis, optic neuritis, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins [†]	Limbic, hypothalamic, brainstem encephalitis (infrequently PCD)	Germ-cell tumours of testis, non-SCLC, other solid tumors
Anti-amphiphysin	Stiff-person syndrome, PEM, limbic encephalitis, myelopathy	SCLC, breast
Partly characterised paraneoplastic antibodies *		
Anti-Tr	PCD	Hodgkin's lymphoma
Anti-Zic 4	PCD	SCLC
mGluR1 [‡]	PCD	Hodgkin's lymphoma
ANNA3	Various PND of the CNS	SCLC
PCA2	Various PND of the CNS	SCLC
Antibodies that occur with and without cancer association		
Anti-NR1/NR2 of NMDA receptor [‡]	Characteristic encephalitis [§]	Teratoma (usually in the ovary)
Anti-VGKC [‡]	Limbic encephalitis, PNH (neuromyotonia), other	Thymoma, SCLC, other
Anti-VGCC [‡]	LEMS, PCD	SCLC
Anti-AChR [‡]	MG	Thymoma
Anti-nAChR [‡]	Subacute pandysautonomia	SCLC, others
Anti-GAD	Stiff-person syndrome, cerebellar ataxia, limbic encephalitis, other	Thymoma, other

PEM=paraneoplastic encephalomyelitis. PCD=paraneoplastic cerebellar degeneration. PSN=paraneoplastic sensory neuronopathy. SCLC=small-cell lung cancer. PND=paraneoplastic disorder. mGluR1=metabotropic glutamate receptor 1. NMDA=N-methyl-D-aspartate. PNH=peripheral nerve hyperexcitability. VGKC=voltage-gated potassium channels. VGCC=voltage-gated calcium channels. AChR=acetylcholine receptor. nAChR=neuronal AChR. LEMS=Lambert-Eaton myasthenic syndrome. MG=myasthenia gravis. GAD=glutamic acid decarboxylase.

* Well characterised antibodies are those directed against known antigens or that have been identified by several investigators.

[†] The main antigen is Ma2; patients might develop antibodies to Ma1.

[‡] Antibodies that react with cell-surface antigens.

[§] Anti-NMDA receptor encephalitis: prominent psychiatric symptoms, memory loss, decreased consciousness with frequent hypoventilation, autonomic instability, and dyskinesias.

Table 3

Differential diagnosis of PND

	Differential diagnosis	Other possibilities in patients with cancer
Paraneoplastic cerebellar degeneration	Alcohol-related Vitamin deficiency (thiamine, vitamin E) Toxins (anticonvulsants, other) Infectious or postinfectious cerebellitis Miller-Fisher syndrome GAD-associated cerebellar ataxia Gliadin-associated cerebellar ataxia Creutzfeldt-Jacob disease	Cerebellar metastasis Chemotherapy toxicity (fluorouracil, cytarabine)
Opsoclonus-myoclonus	Infectious, postinfectious encephalitis Hyperosmolar coma Side-effects of drugs (amitriptyline, lithium, phenytoin and diazepam, other) Intracranial haemorrhage Systemic disease (AIDS, sarcoid, viral hepatitis, celiac disease)	Intracranial tumours or metastasis Hydrocephalus
Limbic encephalitis and variants	Herpes simplex virus encephalitis Sjögren's syndrome Hashimoto's encephalopathy Systemic lupus erythematosus Toxic-metabolic encephalopathy Korsakoff's syndrome (thiamine deficiency) Syphilis Primary angiitis of the CNS	Brain metastasis Herpesvirus 6 limbic encephalitis (in particular after bone marrow transplantation) Low grade glioma Gliomatosis cerebri

GAD=glutamic acid decarboxylase.

Table 4

Recently identified antibodies in patients with cerebellar degeneration, opsoclonus-myoclonus, and limbic encephalitis

	Syndrome	Tumour	Number of cases	Comments
CARP VIII ⁵⁹	PCD	Melanoma	1	CARP VIII is highly enriched in the cerebellum
Zic1, Zic 4 ⁶⁰	PCD	SCLC	18	Mutations of Zic1 and Zic4 result in cerebellar malformation (Dandy-Walker)
PKC γ ⁶¹	PCD	Non-SCLC	1	Missense mutations of PKC γ result in autosomal dominant cerebellar ataxia (SCA14)
Proteasome ⁶²	PCD	Ovary, other	12	All patients had anti-Yo antibodies
Neuroleukin ⁶³	Opsoclonus	No tumour	2	Post-streptococcal
Gliadin, IgA subtype ⁶⁴	Opsoclonus	No tumour	1	Celiac disease; patient also had endomysial and CV2 antibodies
Adenomatous polyposis coli ⁶⁵	Opsoclonus	2 SCLC, 2 idiopathic	4	Protein highly expressed in brainstem, cerebellum and hippocampus; 2/4 patients had opsoclonus, the other 2 had nystagmus, diplopia, ataxia
Zic2 ⁶⁵	Opsoclonus	SCLC	1	Member of the Zic family of proteins, involved in cerebellar development (see above)
Anti-BR serine/threonine kinase 2 ⁶⁶	LE	SCLC	1	..
Antibodies to CRMP3-4 ⁶⁷	LE	Thymoma	1	The affected patient also had GAD antibodies
Adenylate kinase 5 ⁶⁸	LE	No tumour	2	Refractory to treatments
GluRe2 ⁶⁹	LE	Ovarian teratoma	1	Described in many other disorders. Different from anti-NR1/NR2 heteromers of NMDA receptor

CARP=carbonic anhydrase-related protein. PCD=paraneoplastic cerebellar degeneration. PKC=protein kinase C. SCLC=small-cell lung cancer. SCA=spinocerebellar ataxia. LE=limbic encephalitis. GAD=glutamic-acid decarboxylase. CRMP=collapsin-response mediator protein.

Table 5

Limbic encephalitis—clinical features and response to treatment in relation to antibodies and antigen location

	Classic antibodies: Hu, Ma2, CV2/CRMP5, amphiphysin (intracellular antigens)^{47,93-95}	Antibodies to VGKC (cell-surface antigen)^{14,96}	Antibodies to NR1/NR2 heteromers of NMDA receptor (cell-surface antigen)¹⁸	Antibodies to other cell-membrane antigens⁹²
Predominant antibody reactivity with hippocampus	No; these antibodies react with all neurons of the neuraxis	Moderate; these antibodies also react with cerebellar and cerebral cortex	Yes, particularly when CSF is used	Yes, along with reactivity with the molecular layer of cerebellum
CSF inflammatory changes	Common	Rare or mild	Common	Common
Hyponatraemia	No, except for SCLC	Common	No	No
Symptoms different from classic limbic encephalitis	Several according to the type of antibody	Neuromyotonia, Morvan's syndrome, REM sleep disorders, epilepsy	Psychosis, seizures, decreased level of consciousness, autonomic instability, hypoventilation, dyskinesias	Rare; the clinical picture is typical of limbic encephalitis
Initial MRI findings	Common FLAIR hyperintensity in medial temporal lobes (typical findings)	Frequent typical findings	Normal or increased FLAIR signal in cerebral or cerebellar cortex, transient meningeal enhancement. In about 25% of cases: typical findings	Typical findings and/or increased FLAIR signal in focal cortical regions
Commonly associated tumours	Depends of antibody type (see text)	In 20% of cases: thymoma; less frequently SCLC	Teratoma of the ovary	Tumours of the thymus, Hodgkin's lymphoma, SCLC, no tumour
Expression of the target antigen by the associated tumour	Yes	Unknown	Yes	Unknown
Response to treatment (tumour removal or immunotherapy)	Rare, except 35% of patients with anti-Ma2 encephalitis	~80%; limited response if associated with SCLC	~70%	~60–70%; no response if other antibodies (eg, Hu) are present
Antibody titres	Detectable for months or years (poor clinical correlation)	Decrease with clinical improvement	Decrease and disappear with clinical improvement	Decrease with clinical improvement

VGKC=voltage-gated potassium channel. SCLC=small-cell lung cancer. FLAIR=fluid-attenuated inversion recovery. Adapted with permission from Lippincott Williams and Wilkins.⁹⁷