Paraneoplastic Neurologic Syndromes – An Update on Current Understanding and Future Perspectives

Wolfgang Grisold,[1] Bruno Giometto,[2] Stefan Oberndorfer[3] and Roberta Vitaliani[4]

1. Professor and Clinician, Neurology Department, KFJ Hospital, Medical University of Vienna and Ludwig Boltzmann Institute for Neuro-oncology; 2. Head, Department of Neurology, Ca' Foncello Hospital, Treviso; 3. Clinician, Neurology Department, KFJ Hospital, Medical University of Vienna and Ludwig Boltzmann Institute for Neuro-oncology; 4. Consultant, Department of Neurology, Ca' Foncello Hospital, Treviso

Abstract

Paraneoplastic neurological syndromes (PNS) are remote effects of tumours on the nervous system. They can strike at single or at multiple sites of the central nervous system (CNS) and the peripheral nervous system, and often appear before the detection of cancer. PNS can be disabling and debilitating and may be either an additional burden to cancer or the cause of death. The PNS Euronetwork group has collected a series of approximately 1,000 patients in several European centres. This study is the largest systematic series of patients with PNS and, for the first time, can answer questions about the most frequent PNS, their detailed symptoms, associated antibodies and the types of underlying tumours. The clinical course and laboratory findings for many PNS suggest an autoimmune pathogenesis; however research into this heterogeneous immunological relationship has been evolving over recent decades. The classical syndromes are antigen-target-oriented syndromes such as myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS) and ion channel-mediated diseases. Onconeuronal antibodies constitute a large group of PNS, characterised by the appearance of specific antibodies, defined clinical signs and often an association with specific tumours. In recent years, a new group of antibodies directed at surface antigens as receptors has been identified. Finally there is a long list of 'other' PNS, which are evident to clinicians but which have no pathogenetic explanation. Examples include the mild terminal neuropathies and sarcopoenia in cancer patients. In addition to the emerging classification based on pathophysiology, other new syndromes and symptoms have appeared, including apnoea in brainstem encephalitis, a neuropsychiatric spectrum of limbic encephalitis and increased knowledge about LEMS. Two important aspects warrant attention: some PNS respond to therapy and not all paraneoplastic-like syndromes are tumour related. This view is based on the current understanding of immune pathogenesis and on the enlarged spectrum of PNS.

Keywords

Paraneoplastic neurological syndromes, onconeuronal antibodies, ion channel antibodies, surface antibodies, psychiatric manifestations, limbic encephalitis, therapy

Disclosure: The authors have no conflicts of interest to declare.

Acknowledgement: Joanne Fleming assisted with the text preparation. Grants QLG1-CT-2002-01756 and LSSM-CT-2005-518174 from the Paraneoplastic Neurological Syndromes European Commission (PNS-EURONETWORK).

Received: 28 September 2010 **Accepted:** 9 November 2010 **Citation:** *European Neurological Review*, 2010;5(2):73–6 *DOI:10.17925/ENR.2010.05.02.73*

Correspondence: Wolfgang Grisold, Neurology Department and Ludwig Boltzmann Institute for Neuro-oncology, KFJ Hospital, 1100 Vienna, Austria.
E: wolfgang.grisold@wienkav.at

Paraneoplastic neurological syndromes (PNS) were first described in the 20th century. A summary of observations dating back to 1982 was published in the seminal book by Henson and Urich.[1] The detection of autoantibodies for myasthenia gravis (MG) and later for Lambert-Eaton myasthenic syndrome (LEMS), marked a new era of antibody-mediated disease. Several onconeural antibodies were described by the group at Memorial Sloan Kettering[2] and were subsequently named according to the initials of the patients (Hu, Yo, Ri, etc.) in whom they were discovered. These remain a mainstay of PNS. The group at the Mayo Clinic provided different terminology.[3]

In recent years, two more pathogenetically different types of immune-mediated neurological paraneoplastic syndrome have been described. The first is a group of diseases with antibodies against ion channels (voltage-gated potassium channels; VGCK). This group of diseases behaves like the target-specific antibodies – the effect of autoantibodies on potassium channels was described by Hart et al.[4] The new class of antibodies is directed against the neuropil – in particular against synaptic surface antigens such as N-methyl-D-aspartic acid (NMDA), gamma-aminobutyric acid (GABA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA).[5,6] Clinically, they are often associated with psychiatric disease and present with neurologic core symptoms such as seizures.[7] However, this new class does have three particular aspects: they are not always paraneoplastic, but do present as autoimmune syndromes; they can be treated and are potentially reversible; and they constitute a new spectrum of diseases, which may be related to several other diseases, in particular psychiatric diseases. The important question for clinicians seeing patients with malignant disease is to decide whether the cause of a patient's condition is metastatic, metabolic, neurotoxic or infectious. Due to the rarity of PNS, this answer cannot accurately be given. Between 2002 and 2008 the PNS Euronetwork project[8]

Table 1: Paraneoplastic Neurological Syndromes Frequency of Tumours

Type of Tumour	%
Small cell lung cancer	38
Ovary	10
Breast	10
Non-small-cell lung cancer	8
Non-Hodgkin's lymphoma	3
Hodgkin's lymphoma	3
Thymoma	3
Prostate	2.6
Unknown primary	2

Source: Giometto et al., 2010.[8]

Table 2: Most Frequent Paraneoplastic Neurological Syndromes (PNS) in the PNS Euronetwork Database

Type of PNS	Patients (n=979)	%
Paraneoplastic cerebellar degeneration (PCD)	238	24.3
Limbic encephalitis (LE)	98	10
Paraneoplastic encephalomyelitis	55	5.6
Brainstem encephalitis	55	5.6
Opsoclonus/myoclonus	23	2.3
Motor neuron disease (MND)	20	2
Sensory neuronopathy (SSN)	238	24.3
Acute inflammatory polyradiculopathy	16	1.6
Chronic inflammatory polyradiculopathy	13	1.3
Dysautonomia	51	5.2
Lambert Eaton myasthenic syndrome (LEMS)	43	4.2
Dermato-/Polymyositis	14	1.4

PNS = paraneoplastic neurological syndrome.
Source: Giometto et al., 2010.[8]

collected about 1,000 patients with definite PNS according to the Graus criteria.[9] This study showed lung cancer to be the most common malignancy (see *Table 1*), subacute sensory neuronopathy (SSN) and paraneoplastic cerebellar degeneration (PCD) as the most frequent syndromes and Hu and Yo as the most frequent onconeuronal antibodies. This distribution, which potentially could be biased by the participating centres and types of disease, is a systematic overview (see *Table 2*).[8] The study also detected 43 cases of LEMS and 10 cases of neuromyotonia, which are classic immune-mediated diseases. The surface antibodies were not available at the time of the PNS Euronetwork study. It is important that neurologists seeing patients with cancer are aware not only of the spectrum of PNS, but also of differential diagnoses, particularly in patients with signs of encephalitis such as infectious and inflammatory diseases, neoplasms of the brain, vascular (in particular hypoxic) damage, seizures, autoimmune disorders and toxic metabolic diseases such as Wernicke's encephalopathy. The presentation of the surface-antibody-associated diseases (e.g. NMDA encephalitis) also could suggest a primarily psychiatric disease, including those presenting as catatonia.

Paraneoplastic Neurological Disease Subgroups

For the purposes of this article, PNS will be classified into four subgroups based on pathogenetic criteria.

Classical Target-oriented Immune-mediated Diseases

In neurology the classic target antibody-mediated diseases are MG, LEMS and neuromyotonia. Antibody-mediated diseases are fairly well understood, although some details are still missing. MG, which can only be considered a PNS of thyoma, has been the pattern for immune models of PNS. In MG, MuSK antibodies have been described in addition to the acetylcholinesterase antibodies, and other antibodies still may be detected in seronegative MG. LEMS is an interesting neuromuscular transmission disorder, affecting the presynaptic calcium channels. It can appear as a paraneoplastic syndrome, or as an autoimmune syndrome. As early as 1988, O'Neill[10] reported that the ratio of incidences of neoplastic to non-neoplastic LEMS was approximately 50:50. These data seem to be confirmed by the time course and more criteria appear, which make it possible to distinguish between the two types of LEMS.[11] Neuromyotonia was described by Hart et al.[4] in the PNS study. It is a nerve hyperexcitability syndrome of the presynaptic endplate. It is also known as Morvan's syndrome, neuromyotonia and continuous muscle fibre activity (CMFA) syndrome. Antibodies against potassium channels have been described[4] and animal experiements have shown that the disease can by transmitted by antibody transfer. Based on these observations, additional aspects, such as dysautonomia, hyponatremia, sleep disorders and psychiatric disorders – in particular limbic encephalitis (LE) – have been found. The antibodies are directed against potassium channels and in several cases go beyond causing neuromuscular disease to encompass CNS symptoms (LE), or autonomic syndromes such as hyponatremia and hyperhydrosis.[12] LE seems to be related to antibodies against the Kv1.1 subunit of the potassium channel, whereas symptoms of neuromyotonia and Morvan's syndrome are more closely related to antibodies to the Kv1.2 channel.[5]

Onconeuronal Antibodies

The description of onconeuronal antibodies has been very useful for studies of PNS. A pragmatic definition and classification of PNS[9] was made by the PNS Euronetwork group. Based on this consensus, the PNS Euronetwork database was used to analyse in detail diseases associated with onconeural antibodies. The database contains not only the number of syndromes, antibody types and tumour types , but also detailed descriptions of clinical symptoms and several paraclinical aspects.[8] Despite these well-described features, the relationship between cause and effect still remains unclear. Transfer between animal and human studies in particular has remained unsuccessful, but pathological studies often demonstrate cytotoxic T-cell infiltrates in the CNS parenchyma and dorsal root ganglia (in neuronopathies). Onconeuronal antibodies anti-Hu, Yo, Ri are most frequently detected, and detection can also be performed by commercial kits. There are three particularly interesting groups: one is a group of less common antibodies – Ma2, Ta, CV2, CRMP5 – which have been investigated by several centres and have high specificity. The second is a heterogeneous group of 'atypical antibodies, which are only detected in individual cases and are often observed in interesting clinical settings. The third are glutamic acid decarboxylase (GAD) antibodies, which can also appear in paraneoplastic diseases that do not fit into this spectrum. *Table 3* shows the distribution of the antibodies detected in the PNS database.[8] The distribution of the onconeural antibodies corresponds to findings in the literature. The ion channel antibodies were routinely examined for voltage gated calcium channels (VGCC) and VGCK, but these were not recorded by all centres. PNS listed without detectable antibodies may represent cases where antibodies are yet to be identified.

Surface Antibodies

Recent developments have led to the discovery of surface antigens, which act either on channels or receptors. Examples of surface

Table 3: Frequency of Onconeural Antibodies

Type of Antibody	%	
Hu	38	
Yo	13	
Ri	5	
CV2	6	
Tr	1.7	
Amphiphysin	3.4	
Ma or Ta	4.5	
VGCC	4	Ion channel
VGCK	1	Ion channel
Atypical	3	
PNS without detectable antibody	18	
Surface antibodies		Not recorded

PNS = paraneoplastic neurological syndromes; VGCC = presynaptic calcium channels; VGCK = voltage-gated potassium channels. Source: Giometto et al., 2010.[8]

antibodies include a diversity of potassium channel, NMDA receptor (NMDAR), AMPA and GABA antibodies, which react with surface antigens of either channels or receptors and have been described in conjunction with some well-known disease entities, such as LE, and with new psychiatric and neurological diseases. These antibodies are antineuropil antibodies and are directed against the NMDA,[13] AMPA (GluR1/2)[14] and GABA receptors.[15] The spectrum of these diseases is wide and, in addition to psychiatric manifestations, hyperkinesia, hypoventilation and severe autonomic symptoms have been observed.[13] Most cases have been described with NMDAR encephalitis. The full clinical spectrum and treatment responses are not yet clear and a recent study reported a high proportion of patients without a detectable tumour.[16] Accordingly, recently it has been suggested that these syndromes be referred to as 'autoimmune synaptic encephalopathies'[17] since the epitope localisation is not always at channel level and most of them are not paraneoplastic. Indeed, the potassium channel antibodies have been demonstrated to target two secreted neuronal proteins that function as ligands for other proteins. The antigens identified are leucin-rich, glioma inactivated 1 protein (LGI1) and contactin-associated protein-2 (CASPR2). Such synaptic encephalopathies are characterised by extracellular location of epitopes and altered function of receptors after antibody binding. The syndromes are severe but treatable (in contrast to many PNS), and the clinical syndrome has symptoms similar to those seen in animal models of pharmacological or genetic dysfunction of the related receptors. Indeed, linkage analysis has shown that mutations in LGI1 genes cause autosomal dominant lateral temporal lobe epilepsy.[18]

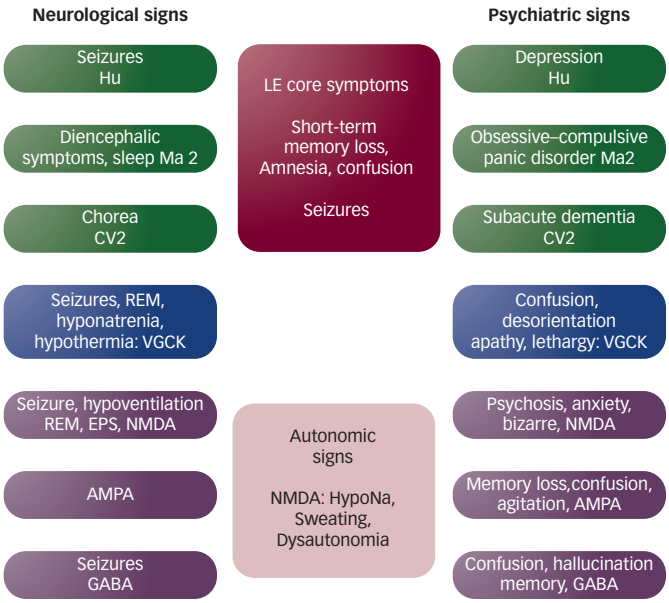
Others

Despite the many classifications and descriptions available, several phenomena – which can be clearly described as 'paraneoplastic' – are yet to be fully explained. Three examples include paraneoplastic neuropathy, terminal neuropathy and cancer cachexia.

Paraneoplastic Neuropathy

The PNS Euronetwork database has revealed that SSN is one of the most frequent PNS[8] and that asymmetry, onset in the upper extremities and characteristic sensory ataxia can be confirmed in most cases that are identified. A considerable number of patients with SSN (117/238) also showed motor involvement, thus prompting the introduction of the term 'sensorimotor neuronopathy'. It remains unclear what causes this weakness: motor neurone loss or axonal degeneration.

Figure 1: Neurologic and Psychiatric Presentations of Limbic Encephalitis



The core symptoms of memory loss, amnesia and confusion are in the centre. Almost every antibody syndrome has additional specific neurologic and psychiatric features. Autonomic signs seem to be more frequent in the N-methyl-D-aspartic acid (NMDA) and voltage-gated potassium channels (VGCK) types of limbic encephalitis (LE). AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EPS = extrapyramidal signs; GABA = gamma aminobutyric acid; LE = limbic encephalitis; REM = rapid eye movement.

Table 4: Basic Principles of Therapy in Paraneoplastic Neurological Syndromes

Type of PNS	Present Situation	Future Perspective
Classical immune mediated	Therapy: Immune modulation Symptomatic therapies	Ongoing subtyping of MG Subtyping of LEMS Neuromyotonia
Onconeuronal antibodies	Impression of many researchers, that early immune modulation or cancer therapy may influence disease positively – as yet unproven	Further characterisation of onconeuronal antibodies in regard to immunological effect
Surface antibodies	Recent implementation in clinical spectrum Responsive to immune modulation (although not always reversible) Definite enlargement of the spectrum of diseases	Sub-characterisations of antigen-specific tailored therapy
Others	Facts of diseases are well known, for most no remedy	Exploration of pathomechanisms, parallels with other diseases

LEMS = Lambert-Eaton myasthenic syndrome; MG = myasthenia gravis; PNS = paraneoplastic neurological syndromes.

Terminal Neuropathy

Patients with advanced cancer often develop signs of neuropathy. This has been well described as a terminal neuropathy, and consists of mild wasting of muscle, areflexia and few sensory changes. This phenomenon resembles neuropathies that occur in patients with severe disease, particularly infections, and may be caused by weight loss or unidentified metabolic factors.

Cancer Cachexia

Cancer cachexia is well known, but still lacks a satisfactory explanation. Many patients experience weight loss, in particular loss of muscle mass.[19] Weight loss and sarcopoenia are also increasingly observed in other generalised diseases, and these may share a common pathway. For cancer patients it has been postulated that reducing or stopping weight loss may yield a better prognosis.[20]

Enlarged Clinical Spectrum of Clinical Paraneoplastic Neurological Syndromes

The PNS database includes the most frequent PNS syndromes and describes large numbers of clinical characteristics for them, enabling clinicians to make judgements based on the results of a large observational study. However, the new recently described surface antibodies will increase its clinical spectrum still further.

Brain Stem Encephalitis and Ventilation

Some PNS, particularly those associated with Hu and the new surface antibodies, may have signs of brain stem encephalitis resulting in hypoventilation and even apnoea.[21] This is of practical importance in patient management and may previously have been overlooked.

The Spectrum of Paraneoplastic Psychiatric and Neurological Symptoms in Limbic Encephalitis

The characterisation of psychiatric symptoms[22] will allow for a more precise diagnosis based on clinical presentation. The core symptoms of LE are short-term memory loss and confusion (see *Figure 1*). Several markers based on antibody type exist, and consist of a neurological and a psychiatric presentation.[22] In summary, LE is one disease with several causes and clinical presentations. LE was accurately described in 1960 by Brierley and Corsellis and, concurrently, neuropathological changes also were found predominately in the temporal lobe. Two new aspects have emerged in recent years: LE can have different clinical presentations and can be associated with seizures, hyponatremia, sleep disorders and a variety of other antibody-dependent specificities. Pathogenetically, LE can have several causes, including onconeuronal antibodies (Hu), ion channel antibodies, surface antibodies (NMDA etc), and may not be associated with apparent inflammation.[23] Several types of LE respond to therapy and have in fact become treatable conditions.

Therapy

There are several considerations regarding the treatment of PNS. First, the underlying tumour should be treated using surgery, radiotherapy and, frequently, chemotherapy. In what way classic tumour removal improves the condition of patients in the presence of ongoing autoimmune therapy is not clear. Tumour treatment, in particular with chemotherapy, exerts an immunosuppressive effect that may also suppress the PNS. The pathophysiology of PNS differs in the various entities and the underlying neoplasms also differ; in addition PNS are infrequent. Taken together, these factors make conventional studies difficult, if not impossible; however, the pathophysiology of PNS is a clue to viable therapies (see *Table 4*). Classic immune-mediated diseases such as MG, LEMS and the VGCK antibodies seem to respond well, and this has been confirmed by many observations. It is not yet clear how PNS caused by onconeural antibodies should be treated. Most authors recommend using immunosuppression or modulation soon after onset of the PNS, to prevent further disease progression. High-dose steroids, cyclophosphamide, IVIg and plasmapheresis have been presribed for this purpose, but there is a paucity of clinical data to support their use. The new class of surface antibodies (NMDA, AMPA and GABA) seem to have similar behaviour to the classic immune-mediated PNS and respond to conventional immunomodulatory drugs. Recurrence has, however, been reported with some of them, which is suggestive of an ongoing process. Novel approaches include the use of biological drugs such as rituximab or natalizumab, but no case series have yet been published.

Conclusion

Knowledge of the occurrence and characteristics of PNS has increased and a large European database has added useful information.[8] In addition to the target-oriented antibodies and onconeuronal antibodies, a new group of surface antibodies has been detected, which are associated with a new spectrum of disease, usually combining neurology and a variety of psychiatric symptoms. Other interesting clinical observations include hypoventilation syndromes in some PNS and the fact that a single syndrome, LE, can be caused by entirely different mechanisms. The key message is that some of the surface antibody syndromes are treatable with immunomodulation and cancer therapy (in cancer-associated types) and may not only improve but even heal the patient. ■

Wolfgang Grisold is a Professor and Clinician in the Neurology Department of the KFJ Hospital, an affiliate of the Medical University of Vienna. He is also Chair of the Ludwig Boltzmann Institute for Neuro-oncology in Vienna. His primary fields of interest are neuro-oncology and neuromuscular diseases. In neuro-oncology his main interests are interactions between cancers and the nervous system.

Bruno Giometto is Head of the Department of Neurology at the Ca' Foncello Hospital in Treviso and the Neuro-Immunology Laboratory of the University of Padova. Dr Giometto has received a grant to co-ordinate the Concerted Action of the European Commission on the Paraneoplastic Neurological Syndrome project, which involves 20 centres in 11 European countries.

Stefan Oberndorfer is a Clinician in the Neurology Department of the KFJ Hospital, an affiliate of the Medical University of Vienna. He is an experienced neuro-oncologist and his interests include brain tumours, the side effects of cancer on the nervous system, in particular metastasis, neurotoxicology and epilepsy and end of life issues in neuro-oncology.

Roberta Vitaliani is a Consultant in the Department of Neurology at the Ca' Foncello Hospital in Treviso. Her research is focused on paraneoplastic syndromes and neuro-oncology. In 2004–2005 she was a research scholar at the Neuro-oncological Institute at Pennsylvania University. Dr Vitaliani obtained her MD in 1999, her specialisation in neurology in 2005 and her doctoral degree in neuroscience in 2009.

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