Paraneoplastic neurological and muscular syndromes

Short compendium
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Throughout this book, text is colour coded as follows:

Clinical features printed in blue
Treatment printed in green

Underlined text is hyperlinked

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Figure 1:
Immunoreactivity of some of the most common oncological anti-neuronal antibodies

Top left: Anti-Hu staining of neuronal nuclei (cerebellar granule & Purkinje cells)
Top right: Anti-Yo staining of Purkinje cell cytoplasam; the red nuclei in the granular layer stained by ethidium bromide
Second level left & right: Anti-Ri immunoreactivity is identical to that of anti-Hu on neurons of the central nervous system. Unlike anti-Hu however, anti-Ri antibodies do not immunoreact with neurons of the peripheral nervous system.
Third level left: Immunoreactivity of anti-amphiphysin (protein of nerve terminals) detected by immunofluorescence on cerebellum. Notice that the cytoplasm of Purkinje cells is negative.
Third level right: The immunoreactivity of anti-CV2 antibodies on cerebellum is mainly restricted to a subpopulation of oligodendrocytes.
Bottom left: A. Anti-Ta (Ma2) immunoreactivity with subnuclear brain structures and in a dot-like pattern
Bottom right: B. Anti-Ta (Ma2) immunoreactivity with large nuclei and cytoplasm of the brainstem & deep cerebellar neurons
Paraneoplastic neurological syndromes (PNSs) are accumulations of clinically recognizable and connected symptoms thought to arise as remote effects of cancer on the nervous system. These syndromes are significantly more frequently occurring in patients with cancer than in those without. Still, the precise initial mechanisms leading to the syndromes are essentially unknown, even though various immunopathological features have been clarified.

**The criterion “remote effects of cancer”** signifies that PNSs per definition cannot be attributable to:
- Mechanical, inflammatory or neoplastic effects in continuity with neoplasms, including metastasis and meningeal carcinomatosis
- Cancer-related cachexia and anorexia
- Neurotoxicity from chemotherapy
- Adverse effects of radiation therapy
- Vascular or metabolic disorders
- Infections
- All other not cancer-related causes

Adhering to this definition, mild or subclinical muscular weakness or peripheral neuropathies are features in up to 20% of patients with cancer. However, a clinically significant PNS occurs in less than 1% of such patients.

**PNSs are heralding neoplasms**
As a rule, such syndromes are early symptoms (or set of symptoms) that might indicate the start of a neoplastic disease before specific symptoms occur (prodromes). The symptoms and signs may even precede the diagnosis of a neoplasm by several months and sometimes years. This may also be true even after an intensive search for a tumour. In such a case, consider one or more follow-up examinations at appropriate intervals.

**Often quite disabling neurologic features**
Another characteristic is that the neurologic features in themselves may be much more disabling that the other effects of the cancer. Although relatively uncommon, the PNSs therefore are important causes of severe and permanent neurologic disability. Early diagnosis of the neurologic disorder and prompt initiation of tumour treatment probably increase the likelihood of neurologic improvement.

**Occurrence of onconeural antibodies**
Several autoantibodies have a syndromic association, although none of them appears to predict a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibody to be detected, each predictive of the same cancer.

The great majority (>90%) of patients with PNSs have circulating onconeural antibodies which can be useful in identifying the neurologic disorder as paraneoplastic and in finding the associated neoplasm. However, such autoantibodies can also be a feature of some patients with cancer and without neurological symptoms. The strongest association between neoplasia and neurological disorders is that between small-cell lung cancer (SCLC) and anti-Hu (Hull) antibodies. The seropositive incidence is about 17% in SCLC patients. Accordingly,
these autoantibodies are *important markers of PNS and neoplasms*.

As a rule: the 'classical' onconeural antibodies (anti-Hu, Yo, Ma2, CV2 (CRMP-5), amphiphysin and Ri) are directed against intracellular antigens and are strongly associated with underlying malignancy. By contrast, onconeural antibodies directed against cell surface antigens (e.g., anti-NMDAR, VGKC, AChR) have a weaker tumour association.

**Discussion**

It is tempting to speculate that PNSs may be attributable to immune responses against tumours that express neural antigens. The majority of the onconeural antibodies are specific for intracellular antigens, and only a minor fraction of them is exposed to extracellular structures, such as receptors and channels (Table 9).

The central and peripheral nervous systems are usually considered immune privileged sites, so the paraneoplastic immune response must be capable of breaching the blood-brain or the blood-nerve barrier in order to cause neurological pathology. The neuromuscular junction (NMJ) is an exception, since no barrier is protecting this location. It is quite uncertain to which extent intrathecal synthesis of onconeural antibodies may account for pathology. The intracellular localization of many paraneoplastic antigens adds further to the difficulty in understanding the putative pathological role of onconeural antibodies. Accordingly, these antibodies may be important diagnostic tools but are not necessarily causing the manifestations of PNS, at least not alone.

The value of antibodies is to protect against foreign agents. They should gain access wherever required, included in the cerebrospinal fluid (CSF) and inside cells. Onconeural antibodies are indeed a feature of both the NMJ and CSF in PNS. As one may expect, there is strong evidence to suggest that active mechanisms are facilitating the passage of antibodies across membranes. The internalization of proteins located in membranes is normally a process of endocytosis as part of a recycling process. Presumably, "internalizing" antibodies enter cells by the same mode, although various other similar mechanisms may be operational as well.

Onconeural antibodies are organ specific. For example, anti-Hu and anti-Ri (Richards) antibodies are both immunoreactive with nuclear structures of the central nervous system, but in contrast to anti-Hu, anti-Ri antibodies do not bind to nuclei of neurons in the peripheral nervous system. Therefore, anti-Hu and anti-Ri are also known as anti-neuronuclear antibodies type one & two (ANNA1, ANNA2), respectively. Likewise, the occurrence of anti-Ri is not associated with any peripheral PNS, while an anti-Hu finding is associated with PNS of both locations. It is also noteworthy that more than nine onconeural antibodies recognize intracellular structures of the Purkinje cells, which are some of the largest neurons in the brain. However, passive or more direct transfer models with purified IgG from such patients have failed to produce any PNS in animals, apart from anti-mGluR1. On the other hand, reports have shown that transfer of specific T-cells provokes neurological disorders in animal models. Therefore, it appears that intracellular antigen related PNSs also involve an autoimmune T-cell component. Accordingly, it is possible that merely, neuronal autoantibodies are markers of a destructive process, or else may signify direct toxicity of the activated immune system.

Associated both with and without neoplasms, it is now possible to diagnose autoimmune synaptic encephalitis. The targets may be cell membrane proteins (receptors and channels), a protein within a synapse (e.g. LGI1) or structures that are expressed presynaptically (e.g. an enzyme necessary for the synthesis of a neurotransmitter). Currently known such autoantibodies are directed to NMDAR, AMPAR, GABAβR1, GlyR...
alpha1, AQP4, LGI1, CASPR2, and GAD. It appears that intrathecal synthesis of specific autoantibodies and CNS infiltration of plasma cells are features of some of these disorders.

As related to autoantibodies to exposed extracellular structures, it is a different story. There is clear evidence to show that such associated antibodies play a direct role in autoimmune disorders of the NMJ and other synapses. Using purified IgG (or monoclonal antibodies) directed to exposed epitopes, passive transfer models have been quite successful in producing direct pathology. There are three major mechanisms. Modulating antibodies appear to signal that a structure is already “outdated”, i.e. it is time to replace it. This may be a factor causing endocytosis ahead of time. Alternatively, the autoantibodies may provoke complement-mediated destruction. The result is a scarcity of antigenic targets. The antibodies may also act as competitive inhibitors of such receptors or channels. Altogether, this autoimmune pathology is quite detrimental to the transmission.

Hypothesis

A dynamic hypothesis may therefore be that PNSs either develop dependent on the synthesis and local influx of autoantibodies or as T-cell mediated autoimmunity, and in many cases maybe combined.

Knowledge is lacking about a variety of co-factors. Genetics may also play a major role. Further studies of PNSs may provide clues to a better understanding of tumour immunology and of how the nervous system becomes involved.

Various other aspects

Since we know the location and function of many of the involved structures of the nervous system, a finding of specific autoantibodies provides an important clue to directly linking such a feature to one or more specific locations of the nervous system. Conversely, the clinical findings may suggest one or more specific autoantibodies to look for. In short, knowledgeable and skilful neurologists are able to recognize the clinical manifestations of neurologic paraneoplastic disorders, and to distinguish them from other causes of neurologic dysfunction in cancer patients. Early diagnosis of a PNS maximizes the likelihood of a favourable outcome of both the oncologic and the neurologic disease.
Short introduction to the immune system

The innate immune system
- This is what we are born with and it is non-specific
- All antigens are attacked pretty much equally
- It is genetically based and we pass it on to our offspring

The adaptive or acquired immune system
- Cell-mediated immunity
- Humoral-mediated immunity

Overall classification
The innate immune system provides essential protection already from birth. The adaptive immune system is there to provide additional protection against various hazards that may happen later in life.

The immune system within a PNS context
The current concept is that the expression of neuronal proteins by the cancer triggers an immune response against the tumour and that is misdirected against the nervous system, resulting in the paraneoplastic disorder. This immune response is characterized by high titer of serum antibodies (often accompanied by cytotoxic T-cell responses) that specifically react with proteins exclusively expressed by neurons and the cancer cells (onconeuronal antigens). Detection of these serum antibodies allows for a major step as a part of the diagnosis of these neurologic disorders as paraneoplastic.

Such autoimmunity often involves pathological mechanisms of the innate immune system and in particular toll-like receptors. Conceivably, however, PNSs may arise either as inadequate innate immunity, as inappropriate adaptive or acquired immunity, or as combined and even more complex autoimmunity. Metaphorically, the occurrence of PNSs may be looked upon as an “own goal”. It is of course quite favourable that the immune system is there to protect against neoplasms, but it is unfortunate when this also implies the nervous system to become malfunctioned. Clearly, the immune system is not perfect.

Model disease
The immunopathogenesis of PNSs is very complex. In order to discover various mechanisms therefore, the study of experimental disorders are important.

If a structure is not protected by any barriers (BBB = the blood brain barrier; BNB = blood nerve barrier) and the antigen is an exposed extracellular molecule, then it is technically more simple to create models. Conversely, there are also sequestered structures in existence, i.e. they are invisible to the immune system due to a BBB or BNB or an intracellular location. In such latter cases, special measures are necessary in order to circumvent these hindrances. A first step may be transfer of encephalitis-inducing T-cells to make the barrier leaky. This may also happen by an immunization using Freund’s adjuvant. Having solved these obstacles, the final steps consist in either immunization with a purified antigen or transfer of disease-provoking agents such as specific T-cells or antibodies (for example purified immunoglobulin or specific monoclonals).

Unprotected locations are at the NMJs. In the peripheral nervous system, there are also less protected areas as follows: distal nerve terminals, nodes of Ranvier, areas close to the cell body, and ganglia. In such cases with more or less easy accessibility, a transfer by various direct routes may be possible: intravenous, intraperitoneal, intrathecal, or by local injection.

In analogy with other autoimmune disorders, a useful categorization of the PNSs is:
1. Antibody (humoral)-mediated
2. T-cell-mediated

Most of them are T-cell-mediated.

Criteria to be satisfied to accept a disorder as autoantibody mediated

1. **Key starting point**: relevant antibodies are present in patients with the disease, although not necessarily circulating
2. **“Smoking gun”**: antibody reactivity results in the clinical phenotype, and loss of structures expressing the antigen
3. **Passive transfer of IgG** from affected patient (or better matching monoclonal antibody) to experimental animal reproduces the phenotype
4. **A model disease**: immunization of experimental animal with purified antigen leads to development of the relevant antibody and subsequently the same phenotype
5. **Amelioration of disease**: reduction in titres of the antibody (e.g., therapy) leads to clinical improvement or stabilization

Table 1a: The following disorders appear to satisfy these criteria, either totally or to a lesser extent

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive myasthenia gravis (SPMG)</td>
<td></td>
</tr>
<tr>
<td>- Paraneoplastic SPMG (thymoma)</td>
<td>Anti-AChR to the nicotinic receptor of adult- and embryonic type</td>
</tr>
<tr>
<td>- Early-onset SPMG</td>
<td></td>
</tr>
<tr>
<td>- Late-onset SPMG</td>
<td></td>
</tr>
<tr>
<td>- Neonatal SPMG</td>
<td></td>
</tr>
<tr>
<td>- Acquired arthrogryposis multiplex in SPMG</td>
<td></td>
</tr>
<tr>
<td>Autoimmune autonomic neuropathy (AAN)</td>
<td>Anti-AChR to the nicotinic receptor of alpha3-type</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome (LEMS)</td>
<td>Anti-vg-Ca-channel of P/Q- and N-type, anti-AChR to the muscarinic receptor of M1-type</td>
</tr>
<tr>
<td>Morvan’s fibrillary chorea</td>
<td>Anti-Accessory proteins at vg-K-channels</td>
</tr>
<tr>
<td>Paraneoplastic limbic encephalitis</td>
<td>Anti-Accessory proteins at vg-K-channels, anti-NMDAR, anti-mGluR1, anti-mGluR5, anti-Amphiphysin?</td>
</tr>
<tr>
<td>Acquired neuromyotonia (Isaacs’ syndrome)</td>
<td>Anti-Accessory proteins at vg-K-channels</td>
</tr>
<tr>
<td>Paraneoplastic ataxia</td>
<td>Anti-mGluR1</td>
</tr>
<tr>
<td>Stiff-person syndrome?</td>
<td>Anti-Amphiphysin</td>
</tr>
<tr>
<td>Paraneoplastic opsoclonus, myoclonus?</td>
<td>Anti-Amphiphysin</td>
</tr>
</tbody>
</table>
Table 1b: Experimental autoimmune encephalitis

- 2004: transfer of T-cells specific for the onconeural antigen Ma1 [Brain 2004; 127: 1822–1830]
- 2012: Lewis rat animal model of Sydenham chorea and related neuropsychiatric disorders [http://www.nature.com/npp/journal/v37/n9/abs/npp201256a.html]

Milestones in experimental disease, including PNSs

A. Without a barrier of protection

- **Myasthenia gravis**
  - Immunization with purified ACHR (rabbit model 1975)
  - Transfer of purified IgG (1975)
  - Transfer of monoclonals (1981)
  - Immunization with peptide sequences of ACHR (1994)
- **LEMS**
  - Transfer of purified IgG (1983)
  - Immunization with cholinergic synaptosomes (1990)
- **Neuromyotonia**
  - Transfer of purified IgG (2003)
- **Autoimmune autonomic neuropathy**
  - Transfer of purified IgG (2004)

B. With barriers of protection

- **Presumed humoral mediated**
  - Pioneer CNS model 2003: passive transfer of mGluR1 antibodies
- **Presumed T-cell mediated**
  - Pioneer CNS model 2004: transfer of T-cells specific for the onconeural antigen Ma1
  - Passive transfer in rats by means of IgG to amphiphysin (2005, 2010)

The role of onconeural autoantibodies

Such autoantibodies are a feature of the serum in more than 90% of patients with PNSs. The finding in itself is strong evidence of a coexisting neoplasm, which currently may even escape detection by other means due to a too small size or a location, which is unfavourable to diagnostics.

The breakdown of tolerance appears to be quite selective, since there is an almost exclusive finding of highly organ-specific onconeural antibodies in PNSs.

An illustrative example:

Polymyositis is associated with coexisting cancer. Due to binding of all the myositis specific and overlap antibodies, there are lesions and repair mechanisms, including local infiltrations with lymphocytes. Accordingly, the immune system is exposed to titin, the largest molecule in the body. Anyhow, anti-Titin antibodies are never a feature of this disorder. On the other hand, anti-Titin antibodies are indeed markers of postsynaptic NMJ disorders associated with myopathy, for example in paraneoplastic myasthenia gravis (thymoma).

A lesson learned is that an already tolerated structure that becomes exposed does not provoke autoimmunity in itself. To doing so, it may have to be located within a “danger zone” (Matzinger’s hypothesis), which in a
PNS context would mean a neoplasm. Although still controversial and also in contrast to “classical” immunology, this theory deals with an extra step - costimulation on peripheral sites - saying that the cells of the body must signal distress (“danger”) prior to awakening the immune system, and that the mere presence of a foreign antigen is not enough for any action to be taken. In short, the danger metaphor involves the use of the innate immune system to break peripheral tolerance possibly leading to activation of the adaptive immune system.

Bypass of T cell tolerance: some initial steps into autoimmunity

Foreign epitopes do provoke useful immune defences. They may come into the body from the environment or arise as neo-antigens. Modification of an already tolerated structure may be an adverse effect of drugs or other environmental agents. The T-cells are on the alert and ready to recognise them upon proper presentation, and a “counterattack” may set in.

Cross-reacting epitopes on the other hand, are targets shared by neoplasms or invading microorganisms and existent structures of the body (molecular mimicry). Mimicry between epitopes of the body and an invader or neoplasm can be classified as “similar” or “dissimilar” dependant on the extent of identity from a biochemical point of view. Accordingly, cross-reactive antibodies, which recognize dissimilar epitopes - comparing that of the provoking invader to the targeted one of the body, may be a case of a structural 3-D configuration in itself being sufficient for binding.

If targets are located intracellularly or protected by barriers, such as the blood-brain/nerve barrier, then supposedly they are invisible (“sequestered”) to the immune system. In such a situation, no autoimmunity but only useful immunoprotection sets in. Unfortunately, if the immune system eventually gains access to such epitopes, then autoimmunity is at play. The triggering event could be a “danger zone” somewhere in the body and even remote from the location of the auto-attack.

Another mechanism in autoimmunity may be epitope spreading (ES), associating such pathology with chronic virus infections or neoplasia. The term ES means the development of immune responses to epitopes distinct from and non-cross-reactive with the dominant primary epitope. In autoimmunity, the process of ES may begin with molecular mimicry which then spread to different epitopes (secondary epitopes) on one protein (intramolecular ES), or to epitopes on other proteins (intermolecular ES). Accordingly, the secondary epitopes, which are often cryptic epitopes on the same molecule or dominant epitopes on neighbouring molecules, are those to which responses arise later. Theoretically, individuals harbouring mutated gene products are more likely to be exposed to cross-reacting autoantibodies due to molecular mimicry or to ES than controls without. The theories about autoimmunity also comprise bystander activation, and superantigens that activate polyclonal groups of T-cells. In particular, activation of cytotoxic T-cells may be an important mechanism. There are two major groups of autoimmune disorders: T-cell- and humoral-mediated ones.

Summary

In short, it appears that in-host tolerated targets are in jeopardy, if special conditions present similar epitopes to the immune system. Such an exposure could be in conjunction with neoplasia or certain infections, thereby giving rise to a “danger zone”. Immunization with a purified substance in Freund’s adjuvant also creates such an area.

It is far beyond the scope of this text to go into all the details. The precise mechanisms are complex and quite often largely unknown.
Short summary of the complexity

- The synthesis of autoantibodies is linked with genetics
- Complex interaction: T-cells, B-cells, cytokines, chemokines, etc.
- A tumour is heterogeneous, i.e. only a part of a neoplasm or its metastases may express neural antigens; and in another case, not at all
- In a specific patient, the target may have to be upregulated prior to becoming antigenic
- The extent of protection against provoked complement attack may vary considerably on various surfaces
A PNS diagnosis requires combined clinical and serological findings
In relation to PNSs, four situations may exist; please see the following paragraphs A to D below. In all these instances, there is strong evidence in favour of the existence of a cancer under development.

A. No onconeural antibodies are found in the serum, even though a PNS is likely
- The sensitivity of the autoantibody assay is too low
- The autoantibody may only be found in the cerebrospinal fluid
- It is a case of not circulating but sequestered autoantibody, i.e. it is only present in situ at the various lesions
- A relevant autoantibody has not yet been discovered
- It is a case of a T-cell-mediated disorder with no particular role of any circulating autoantibodies

Clearly, the fulfilment of other diagnostic criteria is desirable.

B. Onconeural antibodies are found in the serum, although there are no symptoms or signs consistent with a PNS
This is a common situation. Anti-Hu antibodies are a finding in more than 15% of patients with SCLC, but only about 1% does exhibit a significant PNS. A diagnosis always requires clinical manifestations, and serological findings in themselves are not diagnostic of any PNS.

C. Onconeural antibodies are found in the serum, and a humoral-mediated PNS is likely
Assuming that the antibody is an associated one rather than irrelevant, such autoantibodies are directly pathogenic to exposed neurological structures. Therefore, unmistakeably and distinct serological support of the diagnosis is available. The non-finding of autoantibody does not exclude the diagnosis; see alternative A.

Furthermore, in such a case, the clinical severity of the PNS is likely to be proportional to the titre of the autoantibody, enabling a performance of longitudinal monitoring of the disorder also by means of serum samples.

D. Onconeural antibodies are found in the serum, and a T-cell-mediated PNS is likely
A relevant seropositive finding is available, but a broader spectrum of the immune defence must be in operation to cause any neurological disorder such as T-cells, cytokines & chemokines, and other co-factors.

Accordingly, serological evidence supports the diagnosis, but the fulfilment of additional criteria is desirable. Once again, “failure” to detect an autoantibody does not exclude the diagnosis; see alternative A.

The starting point
The typical PNS-diagnostic procedure begins by a patient seeking medical assistance for symptoms evolving at a chronology consistent with such a disorder.

With only few exceptions, the clinical findings should be explicable in terms of a bilateral and symmetrical neurological disorder. This follows by several features. The remote effects are due to malfunction of antigenic structures wherever they are located in the nervous system, and thus characterized by being bilateral and symmetric. The onconeural antibodies and the pathological T-cells are organ-specific. The bloodstream is a common passway at some step. The breaches of barriers are supposedly symmetric and located at the most vulnerable sites.
**Step one**

**A focused clinical neurological examination**

Perform a thorough neurological scrutiny and go as far as possible to document that the findings are bilateral, symmetric and most likely also located to one or more foci as outlined above. Furthermore, take care not to mistake any single element of the findings for another.

- Cognition, personality changes, other mental symptoms: mimicking a psychiatric disorder or more likely of a neurologic nature?
- Mapping ataxia, coordination of movements
- Striated muscles: central or peripheral pattern of paresis; muscle atrophy; myokymia; neuromyotonia; chorea; atetosis; opsoclonus; myclonus. Does rest or exercise influence muscular symptoms? What may provoke or relieve involuntary movements? Consider observations during sleep, etc.
- Polyneuropathy is the most common paraneoplastic neurological disorder, so a very detailed examination is called for
- Examination of reflexes
- Look for signs of autonomic neuropathy
- Video recordings of neurological signs may also be useful – and in particular when viewed by a knowledgeable neurologist

**Step two**

**The finding of onconeural antibodies in serum or CSF**

Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibody to be detected, each predictive of the same cancer.

By the end of this textbook, please find a categorized table showing 'PNS versus onconeural antibodies’, which may be useful in choosing an adequate serological screening. The specific findings of this step may point directly to one or only a few significant first-line tests (cf. also the chapter ‘Onconeural antibody targets ....’ for additional clues), or alternatively, choose a “package” covering more than 60% of the spectrum (Table 9). Multifocal clinical findings are quite likely associated with anti-Hu antibodies.

It is also worth bearing in mind a possible co-existence of more than one of these autoantibodies, so consider an inclusion of all relevant ones. A typical example is anti-Hu together with any of the following: anti-CV2, anti-Amphiphysin, anti-Ri, anti-vg-Ca-channel and anti-Zic4. In such cases, SCLC is the expected underlying finding. Optionally, consider postponement of supplemental tests to a second-line procedure. However, if you are planning a treatment with high-dose IgG, then the infusion of such antibodies may seriously hamper the interpretation of subsequent antibody analyses for a long period. Circumvention of this situation is possible by storage of a sufficient number of serum samples on beforehand.

In diagnosing a humoral-mediated PNS, the finding of a relevant onconeural autoantibody is providing quite strong evidence in favour of the supposed disorder. This is in contrast to T-cell-mediated ones, in which an onconeural marker is only providing indirect evidence of the diagnosis. Moreover, it is not rare to encounter a seropositive patient without any features of a PNS, which is explicable in terms of the immune system trying to combat a neoplasm somewhere in the body, although without causing any harm to the nervous system. With few exceptions therefore, the onconeural antibodies are valuable markers of neoplasm, which may even escape other means of detection at an unfavourable point in time.
**Step three**

**Diagnostics by imagery**

**CT** provides rapid, non-invasive imaging of the CNS.

**MRI** offers better resolution of neural structures than that of CT. Currently, MRI is the preferred first-line choice for detection of autoimmune inflammatory areas, demyelinating plaques, neoplasms, metastases, early infarction, subclinical brain oedema, and much more. For example, visualization of inflammatory, demyelinating, or neoplastic lesions may require enhancement with intravenous paramagnetic contrast agents, such as gadolinium. The use of diffusion-weighted MRI allows rapid and early detection of the various disorders.

As related to MRI, the expected finding in PNSs of the CNS is a bilateral, symmetric and somewhat diffuse pathology. It may be bi-focal such as in a “pure” syndrome of limbic encephalitis, cerebellar degeneration, chorea or athetosis (basal ganglia). Alternatively, it could also be multifocal although still symmetrical. This is the expected finding in two situations: the existence of multiple sites of a targeted specific epitope; in cases with more than one onconeural antibody, there is a situation of different targeted epitopes.

Be aware that in paraneoplastic cerebellar degeneration, MRI typically does not reveal any pathology at the onset or even long time during the course, although it may eventually show atrophy.

**In short:** in a context of PNSs, MRI often serves to exclude that there are unilateral findings such as signs of brain tumour, metastasis, stroke, vasculitis, etc. Asymmetrical bilateral findings would point towards glioblastoma, metastases, inflammatory demyelinating disorder, vascular disease etc., rendering a paraneoplastic diagnosis more unlikely.

**High definition magnetic resonance imaging (HD MRI)** captures images at a much higher resolution than ever seen before. With this new technique, radiologists can shorten scan times and see highly detailed pictures. Although the true value of this new technology of imaging still is unknown, it may turn out to be significant also in the diagnostics of PNSs.

**Positron emission tomography (PET)**

PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. The technology is using radioisotopes with a very short half-life, so a cyclotron must be available not too far away in delivery-time to the PET scanner. PET uses isotopes incorporated into compounds normally used by the organ under examination, for example glucose. Such labelled compounds are known as radiotracers. In neurology, fluorodeoxyglucose (FDG) is a common tracer, and the abbreviation for this imaging is FDG-PET.

**Single photon emission computed tomography (SPECT)**

This imaging technique is using gamma rays, and it is providing true 3D information. Brain SPECT is using technetium-99m.

In relation to paraneoplastic CNS disorders, PET or SPECT may be useful, when ‘classic’ MRI fails to reveal any findings, although they are supposedly there.

Some paraneoplastic CNS disorders are truly multifocal or showing clinical continuity with a pattern that may vary among patients. In such instances PET, SPECT or MRI combined may result in a much more precise mapping of the pathology.
Step four
Find intrathecal evidence in favour of on-going immunological processes and exclude meningeal carcinomatosis

Lumbar puncture can be a helpful tool, since CSF inflammation is a common feature of PNS patients. The likelihood of pathological findings is gradually decreasing by time after onset of neurological symptoms.

Presence of a mass that could precipitate transtentorial or cerebellar herniation constitutes a risk. As a rule therefore, consider CT or MRI prior to any examination of the cerebrospinal fluid (CSF).

Table 2 provides a summarization of the findings
- Increased total protein (hyperproteinorachia) is a sensitive but non-specific measure of disease.
- Elevated immunoglobulin and oligoclonal banding are also frequent findings, although unspecific and a feature in a variety of other disorders, such as demyelinising ones and various infections of the CNS.
- Pleiocytosis - with not too many lymphocytes (usually < 25) - is an expected early finding in about 50%. However, depending on the specific nature of the disorder, pleiocytosis may be present for longer periods. A cell count above for example > 100 should alert you to look for other diseases. Per definition, a finding of malignant cells in the CSF excludes the possibility of a PNS. Sometimes the search for malignant cells may involve consecutive lumbar punctures over time, since the initial ones could be falsely negative.

CSF findings are a reflection of on-going immune processes in the CNS. They fade away along with the eradication of antigenic structures. If immunosuppressive treatment is under consideration, then current CSF pathology is an argument in favour of such a treatment. Please also see the arguments for early treatment in the next chapter. Key word may be a medical urgency.

Step five (neurophysiology)
EEG, evoked potentials, EMG, nerve conduction velocity studies, repetitive nerve stimulation, single-fibre EMG

EEG is a method to detect electrical pathology associated with seizure disorders, sleep disorders, and metabolic or structural encephalopathies. Abnormal wave patterns may be non-specific (for example paraneoplastic epilepsy with epileptiform sharp waves) or diagnostic (e.g. in Creutzfeldt-Jakob disease as a differential diagnosis to paraneoplastic chorea).

Measurement of evoked potentials is a method using visual, auditory, or tactile stimuli to activate corresponding areas of the cerebral cortex, resulting in measurable and distinct focal cortical electrical activity. Computer processing cancels out noise to allow detection of abnormal waveforms. Evoked responses are particularly useful for detecting clinically unapparent deficits, which may also be of interest in the diagnosis of PNSs. For example, consider such an examination in an anti-Hu or anti-CV2 (CRMP5) seropositive patient. Such cases are likely to have a multifocal disorder including areas, which may escape detection by other examinations.

Electromyography and nerve conduction velocity studies are both of great value to identify affected nerves and muscles. It may be clinically difficult to make out whether a muscular weakness is due to nerve, muscle, or neuromuscular junctional disorder. Neurophysiology also enables a more precise location of sensory dysfunctions. In addition, neuropathies can be classified into demyelinising and axonal ones, which has important implications to both a proper diagnosis and adequate treatment.
In addition, more precise detection and correct identification of myokymia, neuromyotonia and myoclonus are tasks for a neurophysiologist.

**Repetitive nerve stimulation** is a good method to diagnose myasthenia gravis (paraneoplastic, thymoma) and the Lambert-Eaton myasthenic syndrome (LEMS). Single-fibre EMG may also be of value.

**Step six**  
**Search for a neoplasm**
- By the end of this textbook, please find a categorized table showing ‘Neoplasms versus onconeural antibodies’, which may be useful in searching for the most common cancers associated with any particular autoantibody.
- The chapter ‘Onconeural antibody targets in the nervous system and neoplasms’ may provide other clues.
- Moreover, all neoplasms associated with any particular syndrome are listed in the various chapters of this textbook dealing with any specific disorder.
- If an onconeural antibody is unmistakably present and currently, a neoplasm cannot be found, then consider supplementary search procedures at suitable intervals. A non-finding of cancer does not rule out a PNS diagnosis, since an autopsy may reveal a relevant neoplasm for the first time.

**Step seven**  
**Systematically, exclude all relevant differential diagnoses**
An important criterion of a PNS is the exclusion of all known other disorders with similar symptoms. The finding of onconeural antibodies may be a pretext to somewhat restricting the search for other diagnoses, and this argument may be either supported or weakened by the outcome of steps 3-6.
Table 2:

<table>
<thead>
<tr>
<th>Cerebrospinal fluid findings in patients with paraneoplastic neurologic syndromes: study of n = 295 such patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu</td>
</tr>
<tr>
<td>58%</td>
</tr>
<tr>
<td>Relative to time of onset of neurological symptoms</td>
</tr>
<tr>
<td>Hyperproteinorachia (protein level)</td>
</tr>
<tr>
<td>Presence of oligoclonal bands</td>
</tr>
<tr>
<td>Pleiocytosis</td>
</tr>
<tr>
<td>Pleiocytosis without hyperproteinorachia</td>
</tr>
<tr>
<td>One or more of these features</td>
</tr>
<tr>
<td>Oligoclonal bands were not found in anti-Tr syndrome (0 out of 3)</td>
</tr>
<tr>
<td>Cell count usually &lt; 25</td>
</tr>
</tbody>
</table>

The data above are for from:

Cerebrospinal fluid findings in paraneoplastic cerebellar degeneration

Arbitrary increasing scale

Months after onset
Therapeutic considerations

An ascertainment of a PNS diagnosis is often heralding the coexistence of a neoplasm by several months before a patient otherwise becomes aware of it. Therefore, actions taken rapidly upon such a classification may significantly improve the chances of a more beneficial outcome of oncologic modalities of treatment than compared with a later perspective. Sometimes the prognosis of a neoplastic disorder may even be more favourable in cases with a co-existent PNS than in those without. A possible explanation may be that the immune system attempts to combat the neoplasm much harder by a broader panel of autoantibodies. This latter aspect however, may not be of much value or comfort to a particular patient, since in themselves - PNSs often are much more disabling than other effects of a tumour. Removal of the neoplasm or at least a reduction of its impact may result in less severe PNS, although once started, such provoked autoimmunity frequently appears to continue in spite of a successful oncologic treatment. If a PNS satisfy the criteria for a humoral-mediated disorder, it follows that the clinical course is proportional to the titres of autoantibodies. Therefore, a beneficial outcome of therapy is more likely, in view of the fact that it is often possible to diminish the synthesis of harmful autoantibodies, or to neutralize / remove them (Table 2, 4 - 6). On the other hand, in cases of T-cell-mediated PNSs, adequate treatment may not be available or only limited benefit achievable, please see under ‘immunosuppression’ below.

Table 2: “Classical” modalities of therapy

<table>
<thead>
<tr>
<th>Enumeration</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>Oncologic treatment (beyond the scope of this text)</td>
</tr>
<tr>
<td>1</td>
<td>Improvement of transmission over synapses by various drugs</td>
</tr>
<tr>
<td>2</td>
<td>Anti-epileptics, extrapyramidal remedy, etc.</td>
</tr>
<tr>
<td>3</td>
<td>Other symptomatic drugs</td>
</tr>
<tr>
<td>4</td>
<td>Intravenous administration of high-dose IgG</td>
</tr>
<tr>
<td>5</td>
<td>Extracorporeal removal of autoantibodies (plasma exchange)</td>
</tr>
<tr>
<td>6</td>
<td>Immunosuppression (typically steroids, azathioprine, often combined; various other agents)</td>
</tr>
</tbody>
</table>

General therapeutic considerations

Myasthenia gravis is the prototype of antibody-mediated autoimmunity in neurology. The experience related to the remedy of this disorder has been developed over decades and should at least be applicable to the PNSs listed in Table 1.

Longitudinal monitoring of a disorder by antibody measurements

It is possible to monitor the severity of the disorders of Table 1 both efficiently and conveniently by means of consecutive measurements of the relevant titres of serum autoantibodies at suitable intervals. This allows for timely adjustments of the treatment.

Unfortunately, T-cell-mediated autoimmunity is not proportionate to serum titres of antibodies.

Choice of therapy

Table 2 proposes some principles of a rational and efficient treatment of PNSs. Oncologic therapy serves a double purpose. Evidently, a treatable cancer should undergo an expert-choice of treatment with documented effect. In addition, any removal / reduction of neoplastic tissue may help to stop or at least diminish the impact of such provoked autoimmunity.
**Antibody removal**

In T-cell mediated disorders, treatment option 5 (Table 2) is not really having any spectacular effect, whereas it may be quite efficient in the autoantibody-mediated ones. Therefore, this may be a proper choice in cases of rapidly increasing severity or crises in such PNSs (Table 1).

Since steroids and *for example* azathioprine may take many weeks and sometimes months to reach their maximum capacity of benefit, sessions of plasma exchanges may also be an important remedy during the waiting time for an accomplishment of such an effect. Likewise, if sufficient control is unlikely to occur following treatment option 6 (Table 2), then maintenance removals at suitable intervals are to be considered. Unfortunately, this may also be the proper (only?) choice in cases with bad tolerance to immunosuppressants.

A treatment of one plasma volume during each session often results in an about 75% removal of the circulating pool of autoantibodies. Subsequently of course, antibodies from the extravascular compartments gradually filter back into the bloodstream. A series of removals with one or a few days in between each session is therefore often the method of choice. There appears to be a remarkable tolerance to the original plasma exchange procedure with replacement of only albumin and water as well as to the newer immunosorption techniques.

Usually, repair of the affected structures sets in right after the start of such treatment, and benefit is often observable within days or weeks. The so-called “Lazarus effect”, *i.e.* a severely paralyzed patient is able to walk immediately after the first plasma exchange, is attributable to the immediate removal of blocking antibodies. Unfortunately, the synthesis of autoantibodies continues in spite treatment option 5. As a rule of thumb therefore, one may expect 4-8 weeks of lasting effect, where after it tapers off.

**High-dose IgG**

The prevailing theory about the effect of high-dose IgG (IVIG) is that an infusion of anti-idiotypic antibodies results in a neutralization of autoantibodies.

Since only a minor fraction of the substances is thought to have any effect, and the remaining compounds to be either superfluous or to cause adverse effects, technical improvements of this method are warranted. This may happen by purification, safely and adequately eliminating unwanted parts. On the other hand, the benefit of high-dose IgG may also be attributable to a somewhat broader spectrum of substances. Currently therefore, one is left with a treatment using the whole mixture of IgG. In the treatment of PNSs, this theoretical aspect of a broader mode of action may be of a particular significance. Unfortunately, high-dose IgG treatment is quite expensive.

If IVIG proves to be of benefit, the duration of the effect will probably only last weeks or a few months, where after a relapse is expected to occur. This may call for a repeated intravenous high-dose IgG session and probably on a full scale, rather than a booster like in the Guillain-Barré syndrome, the rationale being an on-going cancer and not a past infection.

**Immunosuppression**

The experience from long-term treatment of myasthenics makes it clear that every effort must be made not to lose immunosuppressant control by an administration of a too low dose, since once lost it may be quite difficult to achieve stable remission again. Unfortunately, all of the currently available immunosuppressive drugs are symptomatic, so such therapy must be kept at an efficient level and as
long as needed. The principle – or difficulty – is to find an optimal balance between the required minimal dose and the risk of serious adverse effects. Furthermore, this must be worked out in a long-term perspective.

The experience with steroids and Azathioprine is long. Methotrexate, Cyclosporine and Cyclophosphamide are other drugs with documented benefit, although also with a substantially higher risk of adverse effects. Tacrolimus is a newer and maybe promising drug, although the experience with this substance is somewhat more limited in neurology.

*Immunosuppression is the primary treatment of choice in T-cell-mediated disorders.*

**Therapeutic keywords in T-cell mediated autoimmunity:**
- Often a medical emergency
- Early destruction of the microenvironment around neurons or neuronal death
- Do not hesitate too long before offering such therapy
- A patient may sooner or later be left with no therapeutic remedy

**Another concern in relation to PNS**
- The legitimacy of immunosuppression in a patient with cancer

**Other modalities of therapy**
Also in relation to PNSs, such symptomatic treatment *(Table 2, 1 - 3)* follows the usual procedures.

**Newer options for treatment**
- A chimeric monoclonal IgG1-kappa antibody, Rituximab, that binds specifically to the CD20 antigen and mediates B cell lysis, may be beneficial to temporarily decrease synthesis of harmful autoantibodies
- Protection against harmful effects of the membrane attack complexes (MAC) may be a promising new remedy. Humanized monoclonal antibodies are appearing on the scene. Eculizumab is a new such drug, which is directed to the complement protein C5, and thereby inhibiting terminal complement activation
- Treatment targeting cytokines or chemokines alternatively using antisense suppression of various enzymes may be other options.
Algorithmic approach to diagnosis and treatment of encephalitis with antibodies to intracellular and cell surface neuronal antigens

From: Lancaster E et al. Neurology 2011; 77: 179-189
Morvan’s fibrillary chorea

**Syndromes of the central nervous system**

**Morvan’s fibrillary chorea** is a rare autoimmune synaptic encephalopathy characterized by chorea and sometimes combined with limbic features, myotonia, neuropathy, and perspiration. The true targets of the associated autoantibodies are leucine rich glioma inactivated 1 protein (LG1) or contactin-associated protein-2 (CASPR2), **accessory proteins and integrated in VG-KC complexes**. This disorder appears to fulfil the criteria of an antibody-mediated autoimmunity.

### Clinical features

- **Attacks of involuntary fibrillary contraction (chorea)** in muscles at rest
  - Involving the muscles of the calves, the posterior parts of the thighs, and rarely the trunk
- **Other CNS dysfunction**
  - Limbic encephalitis with loss of memory
  - Insomnia (agrypnia)
  - Hallucinations
  - Disorientation
  - Seizures
- **Neuromyotonia**
- **Hyperhidrosis**
- **Polyneuropathy**

### Course

May improve spontaneously or with immunosuppression

### Associated disorders

- Anti-AChR antibody seropositive myasthenia gravis (SPMG)
- LEMS

### Autoantibodies

- **Anti-LGI1** (leucine-rich, glioma inactivated 1 protein)
- **Anti-CASPR2** (contactin-associated protein-2)
- **(Anti-voltage-gated K-channels)**

  The targets are located at the dentate gyrus of hippocampus and at the neuromuscular junction. In RIA, using 2% digitonin extract of radiolabelled dendrotoxin, antibodies to Shaker types Kv1.1, 1.2, 1.6 are detectable, although not differentiated. Moreover, such VGKC extract are complexed with two other channel-complex proteins, leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis. Therefore, this assay is not specific to anti-VGPC.

- **Anti-DPPX (DPP5)**

  MG, LEMS laboratory:
  - Anti-AChR (adult-type, foetal-type)
  - Anti-Titin
  - Anti-voltage-gated-Ca-channel (P/Q-, N-type)

### Some differential diagnoses

See examples under paraneoplastic choreo-athetosis.

### Treatment

High-dose IgG or plasma exchange
Immunosuppression

### Selected references

Paraneoplastic cerebellar degeneration (PCD)

Paraneoplastic cerebellar degeneration is a classical PNS with a rapidly progressive gait disorder, which eventually stabilizes. It is associated with a great variety of neoplasms and onconeural autoantibodies. Early treatment is of outmost importance, since Purkinje cells may be lost quite soon.

<table>
<thead>
<tr>
<th>Antibodies predominantly associated with PCD</th>
<th>Predominant syndrome</th>
<th>Associated cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Yo (PCA-1) antibodies</td>
<td>PCD</td>
<td>Breast, small-cell lung (SCLC), ovarian, prostatic</td>
</tr>
<tr>
<td>Anti-Tr antibodies</td>
<td>PCD (occasionally: limbic encephalitis, optic neuritis)</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Anti-mGlur1 antibodies</td>
<td>PCD</td>
<td>Hodgkin’s lymphoma, ovarian</td>
</tr>
<tr>
<td>Anti-ZIC4 antibodies</td>
<td>PCD</td>
<td>SCLC, lung adenocarcinoma</td>
</tr>
<tr>
<td>Anti-ARHGAP26 (GRAF)</td>
<td>PCD</td>
<td>Ovarian</td>
</tr>
<tr>
<td>Anti-HOMER3</td>
<td>PCD with ataxia, headache, nausea, confusion</td>
<td>None</td>
</tr>
<tr>
<td>Sometimes Associated With PCD</td>
<td>Ataxia and other findings</td>
<td></td>
</tr>
<tr>
<td>Anti-Hu (ANNA-1) antibodies</td>
<td>Neuritis, PCD, sensory neuropathy</td>
<td>SCLC, lung adenocarcinoma, other cancers</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2) antibodies</td>
<td>PCD, brain-stem encephalitis, paraneoplastic opsoclonus-myoclonus</td>
<td>Breast, SCLC, gynaecologic</td>
</tr>
<tr>
<td>Anti-CV2/CRMP5 antibodies</td>
<td>Encephalomyelitis, PCD, chorea, peripheral neuropathy, uveitis</td>
<td>SCLC, thymoma, other cancers</td>
</tr>
<tr>
<td>Anti-PCA2</td>
<td>Encephalomyelitis, PCD</td>
<td>SCLC</td>
</tr>
<tr>
<td>Anti-Ta (Ma2), Ma1 protein antibodies</td>
<td>Limbic, hypothalamic, brain-stem encephalitis, infrequently PCD</td>
<td>Breast, lung adenocarcinoma, testis, ovarian, other cancers</td>
</tr>
<tr>
<td>Anti-Amphiphysin antibodies</td>
<td>Stiff-person syndrome, encephalomyelitis, PCD</td>
<td>Breast, SCLC</td>
</tr>
<tr>
<td>Anti-VGCC antibodies</td>
<td>Eaton-Lambert syndrome, PCD</td>
<td>SCLC, lymphoma</td>
</tr>
</tbody>
</table>
Overview of paraneoplastic ataxia

Onset
Although varying, PCD often sets in before the diagnosis of a neoplasm.

Evolution
Usually, this disorder rapidly progresses over weeks to months, then stabilization.

General clinical features
Symmetric pancerebellar syndrome with vertigo

Pathology
Loss of Purkinje cells

<table>
<thead>
<tr>
<th>Table 3: PCD-associated autoantibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  Anti-Hu</td>
</tr>
<tr>
<td>B  Anti-Yo</td>
</tr>
<tr>
<td>C  Anti-CV2 / CRMP5</td>
</tr>
<tr>
<td>D  Anti-Ma1</td>
</tr>
<tr>
<td>E  Anti-PCA2</td>
</tr>
<tr>
<td>F  Anti-Tr (PCA-Tr)</td>
</tr>
<tr>
<td>G  Anti-mGluR1</td>
</tr>
<tr>
<td>H  Anti-CARP8</td>
</tr>
<tr>
<td>I  Anti-GAD</td>
</tr>
<tr>
<td>J  Anti-ZIC4</td>
</tr>
<tr>
<td>K  LEMS-associated, anti-vg-Ca-channel</td>
</tr>
<tr>
<td>L  Other autoantibodies</td>
</tr>
</tbody>
</table>

Associated neoplasms and onconeural antibodies
(Only the most common)

- **SCLC**: anti-Hu, anti-CV2, anti-Ca-channel (P/Q-, N-type), anti-ZIC4
- **Ovary (epithelial)**: anti-Yo
- **Breast**: anti-Yo, anti-Ri
- **Hodgkin’s disease**: anti-Hu, anti-Tr

Other investigations

- **MRI** may be unrevealing at onset and even long time thereafter. Eventually and late in the course, atrophy may be revealed, so alternatively consider PET, SPECT or high-resolution MRI
- **CSF**
  - Protein, cells, and IgG moderately high
  - Oligoclonal bands
  - A feature only during the first month after onset, and fading away along with the disappearance of Purkinje cells

Differential diagnoses

- Alcohol related ataxia
- Gluten associated ataxia (anti-TG6)
- Autosomal dominant cerebellar ataxias (ADCA)
- Familial or sporadic ataxia
- Idiopathic late-onset cerebellar atrophy (ILOCA)
- Multiple system atrophy (MSA), cerebellar subtype
- Epstein-Barr virus associated cerebellar encephalitis
- Primary autoimmune cerebellar ataxia (PACA)

A. Anti-Hu syndrome

Clinical features

- Ataxia
- Associated with a variety of other PNS in the central and peripheral nerve system
- Please see elsewhere and in particular paraneoplastic encephalomyelitis (PEM) and sensory neuronopathy (SSN).
Neoplasm: small-cell lung.

Onset: before detection of cancer

Treatment
Oncologic
*Significant tumour reduction may stabilize the neurological features*

Immunotherapy
Is rarely effective

### B. Anti-Yo syndrome

**Gender**
- Females in most of the cases
- Males, only three patients are reported, two with gynaecomastia

**Onset**
Mean 60 years of age
Related to cancer
- Before cancer: 60%
- After start of tumour treatment: 25%
- May begin with tumour relapse: 15%

**Clinical features**
**Ataxia**
- Severe, pancerebellar
- Located to trunk and limbs
- Dysarthria, oculomotor
- Nystagmus, including down beating
- Oscillopsia and diplopia

**Usually, other CNS & PNS systems are not involved.**

**Progression**
The symptoms aggravate over weeks to months, mean two to three months. Eventually, the outcome is non-ambulatory in 95%.

**Survival**
Mean two to six years
*Dependent on tumour type*
- Breast: 100 months
- Gynaecological: 22 months

**Causes of death**
- Progression of neoplasm in 55%
- Neurologic in 35%

**Associated neoplasms**
- Breast
- Ovary: epithelial
- **Male patients**: gastric, parotid, oesophageal adenocarcinoma
- **Metastases**: invasion of regional lymph nodes common (85%)
- **No neoplasm found** in 10%

**Investigations**
Mammography
Pelvic examination and imaging
**Serum**
- Anti-Yo antibody
- Carcinoembryonic antigen (CEA) and cancer antigen (CA) 125
- Titre may decrease after tumour resection

**CSF**
- Protein: mildly elevated
- Cells: mild mononuclear pleocytosis
- Anti-Yo antibody present

**Treatment**
Oncologic
Such therapy does only rarely result in improvement of the ataxia
Immunotherapy
Cyclophosphamide may possibly be of some benefit

### C. Anti-CV2 / CRMP5 syndrome

Ataxia with antibodies to collapsin response-mediator protein 5

**Clinical features**
The symptoms are quite varied
**Cerebellar** (50%)
- Ataxia
- Nystagmus
- Dysarthria

**Limbic encephalopathy** (30%)
- Dementia
- Mental status and mood changes
- Seizures
Opsoclonus/myoclonus (5%)
Movement disorders (15%)
- Basal ganglia: chorea
Cranial nerve disorders (15%)
- Optic neuropathy
- Abnormal olfaction or taste
Myelopathy (16%)
Peripheral nervous system
- Sensory or sensory-motor disorders (45%)
- Autonomic dysfunction (30%), especially isolated gastro-intestinal; also multiple systems
- Polyradiculopathy (5%)
  - Sensory-motor
  - Legs > arms
  - Symmetric
  - Onset: subacute
  - Pathology: axonal loss; inflammation (50%)
Neuromuscular junction (10%)
- LEMS
Other associated syndromes
- Optic neuritis
- Uveitis
- Intestinal pseudo-obstruction

Anti-CV2 / CRMP5 antibody
Antigen
A 66 kDa neural specific protein with homology to UNC-33 and ULIP

Cellular distribution
- Synapse-rich regions of brain and gut
- Small DRG neurons
- Small-cell neoplasms
- Oligodendrocytes: cytoplasm
- Cerebellum, brainstem, spinal cord and optic chiasm

Please note that in some patients, anti-Hu, or anti-amphiphysin, anti-RI, and anti-ZIC4 are features as well.

Investigations
- CSF
  - Pleocytosis (lymphocytes)
  - High protein
- Anti-CV2 / CRMP5 antibodies (IgG)
  - Present in both serum and CSF

Associated neoplasms (especially in the chest)
- Small-cell lung (80%)

- Thymoma (5%)
- Other: uterine sarcoma

Treatment
Tumour removal may result in some improvement

D. Anti-Ma1 syndrome

Typically, in this syndrome there is a combination of cerebellar and brainstem disorders.

Age at onset
- 55-65 years
- Either up to one year before detection of the neoplasms or concurrent with the cancer diagnosis

Clinical features: not uniform
- Cerebellar: trunk and extremities
- Brainstem: EOM limitation, dysphagia
- Other: sensory loss, myokymia

Prognosis: death in about 50%

Antigen
- Ma1 protein
  - 37 and 40 kDa proteins located to neuronal & testicular germ cell
  - Homology to Ma2 (Ta) and Ma3

Tumours: not uniform
- Testis
- Breast
- Lung (large-cell)
- Colon

Pathology
Gliosis of brainstem and cerebellar nuclei; inflammation
E. Syndrome with anti-PCA2 antibodies

**Gender**
- Females in 70%

**Onset**
- 40-85 years of age

**Clinical features**
- Quite varied syndromes
  - Limbic encephalitis: 50%
  - Cerebellar ataxia: 30%
  - Lambert-Eaton myasthenic syndrome: 20%
  - Autonomic neuropathy: 10%
  - Motor syndrome: 10%
  - Stiff-person syndrome
  - No neurologic syndrome: 10%

**Associations**
- Smokers
- Lung cancer (small-cell)

**Antigen**
- Protein: 280 kDa
- Location: neuron-specific.
  - Purkinje cell cytoplasm in soma and dendrites

**Associated antibodies**
- Anti-PCA2 (IgG): serum + low titres in CSF
- Anti-vg-Ca-Channel (P/Q- & N-type)
- Anti-AChR (nicotinic adult- and foetal-types)
- Anti-AChR (nicotinic alpha3-type, autonomic)

---

F. Anti-Tr (PCA-Tr) syndrome

**Gender**
- Males > females (3:1)

**Onset**
- Age: median 61 years; range 15 to 75 years
- Before (70%) or after cancer; also during remission

---

G. Ataxia with anti-mGluR1 antibodies

- Ataxia associated with antibodies to metabotropic glutamate receptor R1. *This disorder appears to fulfil the
Onset: 3 years after neoplasm

Course: progressive ataxia

Clinical features: Pure cerebellar syndrome
- Ataxia: limb, truncal, gait, dysarthria
- Ocular: horizontal nystagmus
- Mental status: normal

Investigations
Antibodies
- Anti-CARP8
  - Tissue staining
    - Cerebellum: Purkinje cell cytoplasm and dendrites
  - Weaker staining
    - Lateral nuclei of thalamus
    - Bronchial epithelial cells
    - Melanomas: one of seven tested
- Location: serum and CSF

Other laboratory
CSF
- Lymphocytosis
- Oligoclonal bands

Neoplasm: melanoma

Treatment: none

H. Ataxia with anti-CARP8 antibodies

Ataxia associated with antibodies to carbonic anhydrase-related protein 8.

Epidemiology: only one patient reported a 77-year-old female

I. Syndrome with anti-GAD antibodies

Please see stiff-person syndrome: variants

J. Syndrome with anti-ZIC4 antibodies

Clinical features
- Ataxia, moderate to severe
- Slurred speech
- Vertigo

Neoplasm: small-cell lung (SCLC)

Antibodies
• Anti-ZiC4
Bearing in mind that SCLC is the associated neoplasm, consider looking for other onconeural antibodies as well. PEM rather than PCD is the most likely diagnosis, should such antibodies also be a feature.

In short, detection of ZiC4 antibodies often associates with
• Anti-Hu or CV2 (CRMP5) antibodies

On the other hand, patients with isolated ZiC4 antibodies are more likely to develop isolated cerebellar dysfunction than those with concurrent immunities.

![K. LEMS-associated](image)

Ataxia associated with Lambert-Eaton myasthenic syndrome.

---

### Antibodies

- Anti-vg-Ca channels (P/Q- & N-type)
- Increased incidence in anti-Hu syndromes

### Neoplasm

small-cell lung

### Treatment

See the Lambert-Eaton myasthenic syndrome.

### L. Ataxia with other autoantibodies

**Antibodies**

- Anti-ARHGAP26 (GRAF), anti-Protein kinase C gamma (PKC gamma)

**Neoplasm**

- ovarian (anti-GRAF)
- non-SCLC (anti-PCK gamma)

---

**Selected references**

Paraneoplastic choreo-athetosis / striatal encephalitis

Paraneoplastic choreo-athetosis is a rare encephalopathy characterized by extrapyramidal features such as chorea & athetosis. Most frequently, this disorder is associated with anti-CV2 (CRMP5) antibodies, rarely with anti-Hu. The diagnosis is only justified, if chorea is the single or predominant sign in association with onconeural antibodies. The more common situation is a much wider spectrum of neurological findings in patients with anti-CV2 or anti-Hu antibodies - see details elsewhere in this book.

However, if the clinical appearance is that of a multifocal paraneoplastic CNS disorder, for example with ataxia, limbic encephalitis, myoclonus and more, then a diagnosis of paraneoplastic choreo-athetosis is rendered unjustifiable, see PCD, anti-CV2 (CRMP5) syndrome.

Associated neoplasm
Small-cell lung cancer (SCLC)

Some differential diagnoses
- Hereditary disorders with chorea, such as Huntington's disease, neuroacanthocytosis. Metabolic disorders such as Wilson disease and others
- Immunologic disorders, for example SLE
- Paraneoplastic: Morvan's fibrillary chorea
- Post-infectious: chorea (subsequent to group-A streptococci)
- Infectious: Creutzfeldt-Jacob disease
- Stroke
- Senile chorea

Treatment
High-dose IgG
Immunosuppression
Oncologic
Possibly, Carboplatin-etoposid cycles or similar drugs to treat the SCLC

Clinical features
- Chorea, i.e. involuntary brief, irregular, unpredictable, purposeless movements that flow from one body part to another without a rhythmic pattern and involving movements over joints
- Athetosis, i.e. involuntary writhing movements particularly of the arms and hands

Associated antibodies
- Anti-CV2 (CRMP5) is the finding in most cases. Sometimes, anti-Hu, anti-Amphiphysin, anti-Ri, and anti-Zic4 are features as well.

Selected references


Paraneoplastic encephalitides

Paraneoplastic CNS disorders:
Whereas a majority of encephalitides are viral in nature, autoim-
mune encephalitis is increasingly being diagnosed and with a va-
riety of aetiologies - **paraneoplastic**, post-infectious, idiopathic.

Table 4:

<table>
<thead>
<tr>
<th>Category of disorders</th>
<th>Paraneoplastic encephalomyelitis (PEM)</th>
<th>Paraneoplastic limbic encephalitis (PLE)</th>
<th>Paraneoplastic brainstem encephalitis</th>
<th>Paraneoplastic myelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional</td>
<td>Often PEM co-exists as part of a broader anti-Hu syndrome</td>
<td>• Subacute sensory neuronopathy (SSN, PSN)</td>
<td>Moreover, PEM may comprise</td>
<td>• Autonomic dysfunction including chronic intestinal pseudo-obstruction</td>
</tr>
</tbody>
</table>

Table 5:
Overview of paraneoplastic encephalitides: autoantibodies vs. neoplasms

<table>
<thead>
<tr>
<th>Short name (alphabetical order)</th>
<th>Alias: anti-</th>
<th>Primary analysis</th>
<th>Associated neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-AGNA SOX1</td>
<td></td>
<td></td>
<td>SCLC</td>
</tr>
<tr>
<td>Anti-AMPA GluR1/2</td>
<td></td>
<td></td>
<td>SCLC, non-SCLC, thymoma, breast</td>
</tr>
<tr>
<td>Anti-Amphiphysin</td>
<td></td>
<td>Yes</td>
<td>Breast, SCLC</td>
</tr>
<tr>
<td>Anti-BRSK2</td>
<td></td>
<td>SCLC</td>
<td></td>
</tr>
<tr>
<td>Anti-CASPR2</td>
<td></td>
<td>Thymoma</td>
<td></td>
</tr>
<tr>
<td>Anti-CV2 CRMP5, POP66</td>
<td>Yes</td>
<td>SCLC, thymoma</td>
<td></td>
</tr>
<tr>
<td>Anti-EFA6A</td>
<td></td>
<td>Ovarian</td>
<td></td>
</tr>
<tr>
<td>Anti-GAD</td>
<td></td>
<td>Yes</td>
<td>SCLC, thymoma, breast, renal, Hodgkin</td>
</tr>
<tr>
<td>Anti-GABA R1 GABBR1</td>
<td></td>
<td>SCLC</td>
<td></td>
</tr>
<tr>
<td>Anti-Hu ANNA-1</td>
<td>Yes</td>
<td>SCLC, non-SCLC,</td>
<td></td>
</tr>
<tr>
<td>*Anti-K-channel VGKC, VGPC</td>
<td>Yes</td>
<td>SCLC, thymoma</td>
<td></td>
</tr>
<tr>
<td>Anti-LGI1</td>
<td></td>
<td>Thymoidea, kidney, thymus, ovarian teratoma lung</td>
<td></td>
</tr>
<tr>
<td>Anti-mGluR1</td>
<td></td>
<td>Ovarian, morbus Hodgkin</td>
<td></td>
</tr>
<tr>
<td>Anti-mGluR5 Morbus Hodgkin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-NMDAR NR1 / NR2</td>
<td>Yes</td>
<td>Teratoma</td>
<td></td>
</tr>
<tr>
<td>Anti-PCA-2</td>
<td></td>
<td>SCLC</td>
<td></td>
</tr>
<tr>
<td>Anti-Ri ANNA-2, Nova-1</td>
<td></td>
<td>SCLC, non-SCLC, breast, ovarian</td>
<td></td>
</tr>
<tr>
<td>Anti-Ta Ma2, PNMA2</td>
<td>Yes</td>
<td>Testicular, ovarian</td>
<td></td>
</tr>
<tr>
<td>Anti-Tr Purkinje cell (Tr)</td>
<td>Yes</td>
<td>Morbus Hodgkin</td>
<td></td>
</tr>
<tr>
<td>Anti-Yo APCA-1, CDR-</td>
<td>Yes</td>
<td>Breast, ovarian, SCLC</td>
<td></td>
</tr>
</tbody>
</table>

33
* LGI1 and CASPR2 are accessory proteins at VGKCs, and are the true targets

**A. Paraneoplastic encephalomyelitis (PEM)**

The term paraneoplastic encephalomyelitis (PEM) comprises several syndromes characterized by neuronal loss, microglial proliferation, inflammatory infiltrates in the CNS and the co-existence mainly of anti-Hu antibodies. Although some patients may have clinical involvement of only one location throughout the complete clinical course, 75% of them present with a multifocal disorder.

**Overview of the general clinical features**

The symptoms and signs reflect the variable anatomic involvement and include:

- **Encephalopathy (limbic encephalitis)**
  This is the second most common clinical syndrome, and it may remain isolated throughout the clinical evolution.

- **Brainstem syndromes (bulbar encephalitis)**
  These features reflect a predominant involvement of the floor of the fourth ventricle and the inferior olives, resulting in vertigo, nystagmus, oscillopsia, ataxia, diplopia, dysarthria, and dysphagia.

- **Myelitis**

- **Autonomic dysfunction**
  The dorsal root ganglia are affected. This is a feature of about 30% of these patients. The most common symptoms are:
  - orthostatic hypotension
  - urinary retention
  - pupillary abnormalities,
  - impotence
  - dry mouth

  Occasionally, there is also chronic intestinal pseudo-obstruction due to damage of the neurons of the myenteric plexus.

- **Subacute sensory neuropathy (SSN, PSN)**
  This is the most common clinical syndrome. In about 20% of the patients, SSN is the only clinical evidence of paraneoplastic disease.

**Associated neoplasms**

Small-cell lung cancer (SCLC) in about 75%

**Associated antibodies**

- **Anti-Hu** (most frequent)
  Particularly in cases presenting with isolated limbic encephalitis throughout the complete clinical course:
  - Anti-CV2 (CRMP5)
  - Anti-Amphiphysin
  - Anti-Ri
  - Anti-PCA2
  - Anti-Yo
  - Anti-ZIC4, less frequent
  - **other antibodies**, see Table 5 and below

**Treatment**

**Oncologic**

*Significant tumour reduction* may stabilize the neurological features.

**Immunotherapy**

Rarely effective

Anyhow, intravenous high-dose IgG, steroids or plasmapheresis may be worth trying, since a few patients do improve.
Paraneoplastic limbic encephalitis (PLE) is a classical PNS with acute or subacute encephalopathy characterized by involvement of the limbic system and a variety of onconeural antibodies.

PLE is a rare disorder characterized by personality changes (autoimmune psychosis), irritability, depression, seizures, memory loss and sometimes dementia. The diagnosis is difficult because clinical markers are often lacking, and symptoms usually precede the diagnosis of cancer or mimic other complications.

The diagnosis of PLE required neuropathological examination or the presence of the four following criteria:

1. A compatible clinical picture
2. An interval of <4 years between the development of neurological symptoms and tumour diagnosis
3. Exclusion of other neuro-oncological complications
4. At least one of the following
   a. CSF with inflammatory changes but no evidence of infection
   b. MRI demonstrating temporal lobe abnormalities
   c. EEG showing epileptic activity in the temporal lobes

Onset
Most frequently (85%), there is a subacute onset of confusion and marked reduction of short-term memory. Seizures are frequent, and they may antedate by months the onset of the cognitive deficits.

Other patients (15%) have a more insidious onset with depression or hallucinations, which can confuse the diagnosis with that of a psychiatric illness.

Clinical features
This disorder presents with a diversity of symptoms including:
Accordingly and in many cases, the symptoms are not restricted to limbic structures. Short-term memory loss or amnesia, disorientation, confusion, depression, agitation, anxiety are typical features.

Typical findings
- Loss of short-term memory (85%)
- Cognitive disturbance (15%)
- Epileptic seizures (50%)
- Acute confusional syndrome (45%)
- Additional psychiatric symptoms (40%)
- Personality change, hallucinations, depression
- Brainstem symptoms (25%)
- Signs of hypothalamic involvement (20%)
- Involvement of other neurological structures (about 40%)

**See also cerebellar syndromes with anti-GAD & anti-PCA2 antibodies and Morvan’s fibrillary chorea.**

### Diagnostic criteria
- Typical clinical symptoms
- Less than four years to tumour diagnosis
- Brain MRI, SPECT or PET showing the typical involvement of hippocampus
- **Exclusion of other diagnoses**
  - In particular, the more common non-paraneoplastic autoimmune limbic encephalitis associated with autoantibodies to vg-K-channels and which disorder, apart from the neoplasm is clinically indistinguishable from PLE with a thymoma.
  - Also exclusion of non-paraneoplastic anti-NMDAR encephalitis (idiotypic or SLE with CNS involvement)

### Other investigations
- EEG
- Cerebrospinal fluid
  - Pleocytosis and oligoclonal bands (in about 60%)

### Associated neoplasms
- Small-cell lung cancer (50%)
- Testicular tumour (20%)
- Ovarian
- Breast cancer (8%)
- Thymoma
- Hodgkin’s disease
- Prostate
- Teratoma
- Thyroid

- Renal cancer (anti-GAD)

### Associated antibodies

#### Lung cancer
- Anti-Hu
- Anti-CV2 (CRMP5)
- Anti-Amphiphysin
- Anti-GAD
- AGNA (anti-SOX1)
- Anti-PCA2
- Anti-AMPAR (GluR1/R2)
- Anti-BRSK2
- Anti-GABAaR1

#### Breast
- Anti-AMPAR (GluR1/R2)

#### Thymoma
- Anti-LGI1
- Anti-CASPR2
- Anti-AMPAR (GluR1/R2)

#### Testis cancer
- Anti-Ta (Ma2) antibodies are a feature in the great majority of patients. Usually, these cases also present with diencephalic and upper brainstem symptoms that identify a characteristic syndrome. This antibody may also be a finding in patients with other neoplasms, such as prostate, ovarian teratoma, breast, and pulmonary adenocarcinoma

#### Ovarian cancer
- Anti-mGluR1
- Anti-LGI1

#### Prostate or breast cancer
- Anti-Yo

#### Hodgkin’s lymphoma
- Anti-Tr
- Anti-mGkuR1
- Anti-mGluR5 (Ophelia syndrome)
- Anti-GAD

#### Teratoma
  - Acute psychiatric symptoms, prolonged disturbance of consciousness, seizures (refractory status epilepticus), autonomic instability, central hypoventilation and various involuntary movements, dyskinesias, dystonia
Anti-NMDAR (NR1)  
**Types of autoimmune anti-NMDAR encephalitis**  
• Of unknown cause (post-infectious?)  
• Paraneoplastic  

**Epidemiology of anti-NMDAR seropositives**  
• Recent research suggests that non-paraneoplastic encephalitis may be the most frequent  
• Anti-NMDAR encephalitis is increasingly recognized in children, comprising 40% of all cases with encephalitis of previous unknown origin  
• In male patients, it appears that teratomas are not a feature. This is consistent with the rare incidence in the testes of pure benign teratomas, accounting for only 3-5% of germ cell tumours. Accordingly and anyhow, they should be searched for  
• Female patients: decreasing frequency of teratomas by age  

<table>
<thead>
<tr>
<th>Female patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group, years</td>
<td>Frequency of teratomas</td>
</tr>
<tr>
<td>Older than 18</td>
<td>55%</td>
</tr>
<tr>
<td>14.1 – 18</td>
<td>30%</td>
</tr>
<tr>
<td>Up to 14</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Particular additional clinical feature**  
• Maybe also excessive daytime sleepiness  
In such cases, decreased / absent hypocretin-1 may be a feature of the CSF  

**Various**  
• Anti-EFA6A (a guanine nucleotide exchange factor)  
• Anti-nCMAg (novel cell-membrane antigens) which is highly expressed in hippocampus and cerebellum  
• Anti-Adenylate kinase 5)  
• Anti-UBE2E1  

• About 40% are seronegative, and the absence of onconeural antibodies does not rule out the diagnosis  

**Treatment**  
*In general (anti-Hu), this disorder rarely improves with treatment.*  

**Oncologic**  
Removal of the tumour may result in a certain degree of reversal.  

**Symptomatic**  
Consider drug therapy of epilepsy and psychiatric symptoms.  

**Immunotherapy**  
• In particular, patients with anti-Ta (Ma2) antibodies or those without detectable onconeural antibodies may benefit  
• Probably, a finding of anti-vg-K-channels or anti-NMDAR also suggests a good response to immunotherapy  
• Vice versa, the presence of anti-Hu antibodies appears to predict a poor response to such treatment  

**Options**  
• Intravenous high-dose IgG  
• Plasmapheresis, which is an obvious choice, if anti-vg-K-channel or anti-NMDAR antibodies are detected  
• Steroids or other immunosuppressants  

**C. Paraneoplastic brainstem encephalitis**  
Paraneoplastic brainstem encephalitis  
Most frequently, this disorder is a part of multifocal pathology:  
Please look elsewhere for the specific features of the various syndromes  
• Paraneoplastic opsoclonus / myoclonus (POM)  
• Paraneoplastic sensory neuropathy (SSN, PSN)  
• Stiff-person syndrome: variants, PERM
Short summary

1. Association with small-cell lung cancer (SCLC)
   The brainstem encephalitis usually also involves other locations of the nervous system (encephalomylitis).

2. Association with breast or gynaecological cancer
   In about 75%, there is also opsoclonus.
   If not so, then:
   - Oculomotor abnormalities, including gaze paresis, nystagmus, abnormal visual tracking, blepharospasm, and abnormal vestibulocular reflexes
   - Truncal ataxia may predominate and cause severe gait difficulty and frequent falls
   - Limb ataxia is usually mild and most patients retain the ability to write and to feed themselves
   - Nausea, dizziness, dysarthria, dysphagia, diplopia, rigidity, parkinsonism
   - MRI brain scans are usually normal.

3. Association with testis cancer and other neoplasms (anti-Ta (Ma2) syndrome)
   Usually combined with limbic encephalitis or diencephalic symptoms
   - Vertical gaze paresis or paralysis
   - Mild to moderate dysarthria, dysphagia, facial weakness

Associated antibodies and cancer
- Anti-Hu: SCLC
- Anti-CV2 (CRMP5): SCLC, thymoma
- Anti-Amphiphysin: breast
- Anti-Ri: breast
- Anti-Ta (Ma2): testis, breast, colon, lung adenocarcinoma
- Anti-GAD: SCLC, breast, thymoma, Hodgkin and non-Hodgkin lymphoma, renal cell carcinoma

Treatment
The syndrome may stabilize or improve subsequent to a successful oncological treatment (e.g. anti-Ta (Ma2)).

Immunotherapy
Although a few patients may benefit, such therapy rarely is effective. In particular however, patients with a finding of anti-Ta antibodies and no findings of other paraneoplastic auto-antibodies are the most likely to improve.
- Steroids or other immunosuppressants
- Intravenous high-dose IgG
- Plasmapheresis

D. Paraneoplastic myelitis/myelopathy

Paraneoplastic myelitis / myelopathy, which may also be a part of more multifocal pathology (PEM)

Anti-Hu-associated
Clinical features

Motor
- Patchy weakness: arms > legs
- May progress to neck
- Fasciculations
- Eventually, respiratory failure

Sensory
- Associated ganglionopathy

Associated neoplasm

Selected references


Paraneoplastic motor neuron disease?

Paraneoplastic motor neuron disease (MND): Several reports indicate that amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), and progressive muscular atrophy (PMA) may develop coincidentally with a cancer. Although still controversial in existence, some cases of motor neuron disease (MND) may therefore be attributable to a paraneoplastic origin.

Clinical features

- **Motor neuron involvement and anti-Hu syndrome**
  In up to 20% of paraneoplastic encephalomyelitis (PEM), MND is also a feature. This MND involves both upper and lower motor neuron, and such neurology may even be an early manifestation. Otherwise, these patients do not differ to any other aspect of PEM without MND.

- **Amyotrophic lateral sclerosis (ALS)**
  ALS may be a feature of oncologic patients, although this is a rare event.

To date, the World Neurological Association does not recognize the existence of paraneoplastic ALS (EL Escorial Criteria for ALS, 1998).

Oncological patients with ALS do not differ from individuals with sporadic ALS.

- No other anti-neuronal antibodies apart from anti-Hu
- Cause of death: motor neuron defiance
- Comparable survival
- Cancer treatment usually does not improve neurological status.
- On the contrary, though, tumour progression might be
slower in patients with concomitant ALS.

- **Primary lateral sclerosis (PLS)**
  - Pure involvement of the upper motor neurons
  - Rare disease observed in women with a breast cancer
  - Also associated with adenocarcinoma in gall bladder and duodenum (anti-Hu positive)

Accordingly, PLS is the most likely candidate in MND, which is attributable to a paraneoplastic origin.

**Course**
- Chronic and progressive
- May eventually turn into a fully expressed ALS
- The coexistent cancer does not modify PLS progression.

**Investigations**
- Consider mammography in a female patient with PLS
- Possibly also anti-Hu in MND

- **Progressive muscular atrophy (PMA)**
  Also called: Subacute motor neuronopathy

**Clinical features**
- Painless lower motor neuron

- **Motor neuron diseases and lymphoproliferative disorders (LPD)**
  MND (ALS, PLS and PMA) has been observed in relation to
  - Waldestrom’s macroglobulinaemia
  - Multiple myeloma
  - Chronic lymphocytic leukaemia
  - Follicular cell lymphoma
  - Hodgkin’s disease

**Summary**
- It is unclear, if the association is coincidental or of significance in LPD
- MND in LPD patients implies a poor prognosis due to MND progression
- Unfortunately, the treatment of the LPD is unlikely to affect the coexisting MND.

**Selected references**
5. **Criteria for the diagnosis of ALS.**
Paraneoplastic opsoclonus / myoclonus (POM)

Paraneoplastic opsoclonus / myoclonus:
This disorder is within the group of classical PNS. Involuntary movements of the eyes and other striated muscles in any direction characterize it. POM is associated with a variety of neoplasms and onconeural antibodies.

Table 7:
The following paraneoplastic clonus disorders are known

<table>
<thead>
<tr>
<th>Category</th>
<th>Paraneoplastic opsoclonus / myoclonus (POM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>POM in children</td>
</tr>
<tr>
<td>B</td>
<td>POM in adults</td>
</tr>
<tr>
<td></td>
<td>Anti-Hu, anti-Yo, anti-Ta (Ma2) syndromes</td>
</tr>
<tr>
<td>C</td>
<td>POM in adults</td>
</tr>
<tr>
<td></td>
<td>Anti-Ri syndrome</td>
</tr>
</tbody>
</table>

A. Opsoclonus / myoclonus in children

Clinical Syndrome
Age at onset: mean about 18 months. Most before the age of five, and rare in children older than 10 years
Gender: males slightly more often than females
Onset: before or after cancer

Neurologic clinical features
Opsoclonus: conjugate saccades.
- Involuntary
- Multidirectional
- Arrhythmic
- Nearly continuous
- High amplitude
- Persist when the eyes are closed and during sleep
- Associated with blinking, myoclonus
- Increases with visual pursuit and voluntary refixation

Myoclonus (brief involuntary twitching of a muscle or of a group of muscles)
Cerebellar ataxia
Dysphagia and more

Note however, that neurologic features are present in only about two percent of these patients with a neuroblastoma

Antibodies
- Anti-neurofilaments
- At other CNS antigens, for example anti-Hu, anti-ZIC4

Differential diagnosis in children with clonus
- Encephalitis: post-viral syndrome, post-infectious autoimmunity e.g. after group-A streptococci
- Toxic: thallium, lithium, amitriptyline
- Diabetic hyperosmolar coma
- Intracranial lesions: other tumours, hydrocephalus, thalamic haemorrhage

Differential diagnoses in children with neuroblastic tumours
• Neuroblastoma, ganglioneuroblastoma, ganglioneuroma
  Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD syndrome)

Epidemiology
Onset age: 35 to 85 years
Male/female rate 1:2

Clinical features
Movement disorder
• Opsoclonus (30%), triggered by visual fixation
• Myoclonus
• Laryngospasm; dystonia (jaw opening or neck)

Cerebellar: ataxia
• The most common feature of an anti-Ri-syndrome (50%)
• Truncal ataxia and gait disorder
• Nystagmus: 35%
• Dysarthria: rare

Other associated disorders in some patients
• Peripheral neuropathy (25%), sensory-motor with subacute onset
• Myelopathy (20%)
• Encephalopathy with confusion and seizures
• Cranial neuropathy: VI; VIII (deafness or tinnitus)
• Visual blurring
• Polyradiculopathy
• LEMS
• Incontinence

Course
• Quite variable
• About 30% become wheelchair-bound one month after the onset
• Less long-term disability than compared with the anti-Yo and anti-Hu syndromes
• Longer survival than in the anti-Yo and anti-Hu syndromes

Associated neoplasms (85%)
• Breast
• Lung (SCLC & non-SCLC)
• Neoplasm discovered before neurological disorder: 15%
• Distant metastases: 10%

Anti-Ri (ANNA2, NOVA1) antibodies
CNS antigens: 55 kDa (NOVA; RNA binding) and 80 kDa proteins
Immunohistochemistry: antibodies bind to CNS, but not to peripheral neurons

B. Opsoclonus / myoclonus in adults: anti-Hu, Yo, Ta (Ma2) syndromes

Clinical features
Opsoclonus and myoclonus
Associated features
• Encephalopathy
• Seizures
• Syndrome of SIADH (inappropriate antidiuretic hormone secretion)

Associated antibodies and neoplasms
• Anti-Hu, anti-amphiphysin: small-cell lung
• Anti-Yo: breast, ovarian
• Anti-Ta (Ma2): testis
• See also anti-Ri syndrome below

Other associations
• Post-viral syndrome

Treatment
Symptomatic
Thiamine
Clonazepam
Immunosuppression
High-dose IgG, prednisone

Remissions: May occur spontaneously

C. Opsoclonus / myoclonus in adults: anti-Ri syndrome
Other associated antibodies (75%):
- Anti-Hu
- Anti-Ta (Ma2)
- Anti-Tr
- ANNA3
- Anti-CV2 (CRMP5)
- Anti-AChR
- Anti-vg-Ca channel (P/Q- & N-type)

Investigations
CSF
- High protein (35%)
- Pleocytosis (40%)

CNS imaging
Normal in 65%, else there may be findings in cortex, brainstem or cauda equina.

Treatment
Most patients experience neurological improvement after tumour-directed or immunomodulatory therapy.

Immunosuppression
Corticosteroids
Intravenous high-dose IgG

Selected references
Paraneoplastic optic neuritis

The characteristic features of this disorder are subacute optic neuritis and retinitis, associated with anti-CV2 (CRMP5). Most frequently, smokers with small-cell lung cancer are at risk. Positive serology obviates the need for vitreous biopsy and expedites the search for cancer.

MRI from an optic neuritis case. T1-weighted and fat-suppressed spin echo coronal through the orbits. Arrows: Enlargement and contrast enhancement of the left optic nerve in the retrobulbar portion

Onset
Subacute in patients aged 50-75 years and typically in smokers

Clinical features
- Vision loss
- Co-existing retinitis with vitreous inflammatory cells in about 30%
- Multifocal neurological accompaniments with superficially resemblance to Devic's disease at presentation (myelopathy)

Investigations
- Serum: anti-CV2 (SCLC); anti-Tr (Hodgkin’s disease)
- Swollen optic discs and field defects
- Vascular leakage, evident at and remote from the disc

- Abnormal electro-retinograms
- Striking vitreous cells with reactive lymphocytosis, predominantly CD4+
- Cerebrospinal fluid
  - Lymphocytes (<35)
  - Elevated protein
  - Multiple oligodonal immunoglobulin bands
  - Anti-CV2 (CRMP5), IgG

Rule out: neuromyelitis optica (NMO) (Devic’s disease) / optic spinal multiple sclerosis (OSMS), for example by testing for anti-Aquaporin4 (AQP4) antibodies. Consider testing for anti-MOG to diagnose anti-AQP4 seronegative recurrent opticus neuritis.

Associated neoplasms
- Small-cell lung cancer
- Lung adenocarcinoma
- Renal or thyroid carcinoma
- Hodgkin’s disease

Autopsy / biopsy
- Full-length CRMP5 protein is identifiable in normal retina and optic nerve by Western blot analyses.
- Photoreceptor cells, retinal ganglion cells, and nerve fibres exhibit immunoreactivity specific to CRMP5.

See also: Paraneoplastic cerebellar degeneration with anti-CV2 (CRMP5) syndrome.
Selected references


Paraneoplastic retinopathy (CAR, MAR)

Paraneoplastic retinopathy:
The clinical appearance is that of acute retinopathy with vision loss, photosensitivity, night blindness and most frequently, a finding of anti-Recoverin antibodies. Cancer-associated retinopathy (CAR) is the common name for this disorder. Melanoma-associated retinopathy (MAR) is another denomination.

Clinical features
- **Visual loss** with unilateral onset, often before detection of the tumour
- **Scotomas**, initially, peripheral and ring, later-on central

Course
Fluctuating and rapidly progressive

Investigations
- **CSF**: normal
- **Electrophysiology**: ERG abnormal, VER normal

Antibodies
- Anti-Recoverin (23 kDa, calcium-binding protein)
- Anti-Heat Shock Cognate Protein HSC 70
- Anti-CV2 (CRMP5)
- Anti-Alpha-Enolase (ENO1)
- Anti-Arrestin
- Anti-TULIP-1
- Anti-Photoreceptor cell-specific nuclear receptor
- Anti-Rod bipolar cell
- Anti-Carbonic anhydrase
- Anti-Trasducin B

Additional info
- The sensitivity of these antibody-tests is as follows: 60% of patients with autoimmune retinopathy (AR); in 40% of CAR cases
- The anti-Photoreceptor is directed to nuclear steroid receptors in the outer layer of retina and other protein bands
- The anti-Rod is a particular feature of (MAR) as well as of colon cancer-associated retinopathy
- The alpha-Enolase target is at the N-terminal region (amino terminal), located in retinal ganglion cells and inner nuclear layer cells
- Anti-ENO1 is also a feature of Hashimoto’s encephalopathy and some gastrointestinal disorders

Associated neoplasms
- Small-cell lung cancer
- Melanoma
- Gynaecologic
- Colon, lymphoma
<table>
<thead>
<tr>
<th>Proposed diagnostic criteria for paraneoplastic (autoimmune) retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong evidence</strong></td>
</tr>
<tr>
<td>- Diffuse retinal atrophy</td>
</tr>
<tr>
<td>- Negative waveform ERG findings</td>
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<tr>
<td>- Anti- Recoverin antibody</td>
</tr>
<tr>
<td>- Response to trial of metyrapone prednisolone (sub-tenons)</td>
</tr>
<tr>
<td>- CME in panretinal degeneration</td>
</tr>
<tr>
<td>- History of cancer (CAR)</td>
</tr>
<tr>
<td>- History of autoimmune disease in 50 % of immediate family</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAR, cancer-associated retinopathy; CME, cystoid macular oedema; ERG, electroretinogram; RP, retinitis pigmentosa

Please also see: [EyeWiki - Cancer associated retinopathy](https://www.eyewiki.org)

### Selected references

Stiff-person syndrome:
The main features of this disorder are slowly progressive stiffness with muscle spasms. Frequently, SPS is associated with anti-GAD antibodies and in such cases likely to being T-cell-mediated. Other SPS cases are associated with anti-Glycine alpha1 receptor (with or without anti-GAD) and may turn out to fulfil the criteria of antibody-mediated autoimmunity. Anti-Amphiphysin, anti-Gephyrin and / or anti-CV2 may be additional findings.

Epidemiology
- Females (70%)

Age at onset
- Childhood or adult
- Anti-GAD antibody positive:
  - Most common 3rd to 5th decades, mean 40 years

Course
- Usually, SPS is slowly progressive (insidious) or static over years
- Occasionally, the onset is rapid
- Focal syndromes may progress to more generalized involvement
- In occasional patients, sudden death may occur due to
  - Cardiac arrhythmias
  - Restrictive respiratory arrest
  - Rapid tapering of intrathecal baclofen

Prodromes
Episodic stiffness or falling, pains and tightness in axial muscles

Clinical features
Stiffness
Especially, the distribution is in axial and proximal limb muscles. Frequently, it is also asymmetric or prominent in one leg. The involvement of limbs impairs walking. There may be lumbar hyperlordosis, limiting truncal flexion.

These features are reduced in sleep, and do usually fluctuate over time as well.

Muscle spasms
May occur spontaneously or are triggered by
- Stretching
- Emotion
- Sensory stimulation
- Fear of open spaces
Typical cause
- Sudden myoclonic jerks that may produce falling
- This is followed by tonic activity that subsides over seconds

Location of spasms
- Arms: extension and pronation
- Trunk: extension
- Legs: extension and mild abduction; foot inversion
- Co-contraction of agonist and antagonists
- Abdominal and thoracic paraspinal muscles
- Spasms may produce little movement due to co-contraction around joints

Consequences and disability
- May be associated with severe pain
- May also be severe enough to cause fractures
- Due to frequent falls, a cane or walker is commonly needed

Relaxation of spasms
- Sleep & benzodiazepines

Reflexes
- Tendon reflexes: normal or increased
- Abdominal cutaneous: may be lost
- Startle responses: increased

Gait: "Tin soldier"

Autonomic dysfunction
Extraocular movements: (only some patients)
- Gaze-holding nystagmus
- Limited abduction
- Vertical and horizontal ocular misalignment
- Deficient smooth pursuit
- Impaired saccade initiation

Otherwise, normal neurologic examination in most SPS patients

Associated neoplasms
- Breast
- Other: lung, thymoma, Hodgkin’s and non-Hodgkin’s lymphoma, myeloma, renal cell carcinoma

Associated disorders
Epilepsy treated with anti-GABA agents, suggests PERM variant.
Diabetes mellitus, type I (30-60%).

Immune disorders
- Thyroiditis (15%)
- Pernicious anaemia (10%)
- Myasthenia gravis
- Ovarian or adrenal failure, vitiligo
- Similar immune disorders may occur in family members

More common with anti-GAD antibodies
HLA: DRβ1 0301 (40-70 %)

CNS pathology
Perivascular inflammation
Spinal cord: neuronal loss
Lateral vestibular nucleus: loss of neurons

Differential diagnosis
Hyperekplexia (Stiff-baby syndrome)
  - Childhood onset: DYT1 gene mutations
Rule out associated pernicious anaemia

Investigations
Serum CK: transiently elevated
ANA (30%).
CSF
- Oligoclonal bands (60%)
- Protein high (20%)
- Pleocytosis: 10% in SPS; 60% in PERM variant

- Normal: 40% in SPS; 10% in PERM variant.
- Anti-GAD antibodies, although usually lower titre than in serum
- Intrathecal anti-GAD synthesis may occur

MRI of the CNS: non-diagnostic

EMG
Continuous action potentials
- Indistinguishable from voluntary activity: normal motor units
- Persist during attempts at relaxation
- Most prominent in axial muscles
- Rhythmic and synchronous persistent 5 - 6 Hz bursts of 50 to 60 ms duration
- Interruption of bursts by spasms with rapid activity; full interference pattern; > 4 sec
- Activity reduced by intravenous diazepam.
- No fibrillations or grouped rhythmic discharges
- Poor relaxation after contraction

Serum antibodies
Apart from the pancreas, GAD65 is only expressed at GABA-ergic nerve terminals, which co-localizes with Amphiphysin and CV2 (CRMP5) while GAD67 is spread evenly throughout the cells. This difference is thought to reflect a functional difference; GAD67 synthesizes GABA for neuron activity unrelated to neurotransmission, such as synaptogenesis and protection from neural injury. This function requires widespread, ubiquitous presence of GABA. GAD65, however, synthesizes GABA for neurotransmission, and therefore is only necessary at nerve terminals and synapses.

Anti-GAD65 antibodies
Prevalence in SPS: 50-90 %.

Anti-GAD67 antibodies
The prevalence of anti-GAD67 is unknown, so currently, the significance of anti-GAD65 versus anti-GAD67 is relatively unexplored.

Anti-GlyR alpha1 antibodies
About 10% of patients with SPS spectrum of symptoms (with or without associated GAD antibodies)

**Anti-CV2 (CRMP5)**

**Anti-Amphiphysin**
Anti-Gephyrin, rarely

**Tissue staining pattern**
- GABA nerve terminals
- Co-localizes with amphiphysin and CRMP5

The levels of anti-GAD antibody titres vary with clinical syndromes
- High in Stiff-man syndrome
- Usually much higher than in CSF

Specificity: more with higher anti-GAD antibody titres

**Anti-GAD antibodies may also be finding in other syndromes**
1. **Palatal myoclonus**
2. **Epilepsy (autoimmune encephalitis)**
   - Therapy-resistant, localization-related
   - Frequency: 15%.
   - Anti-GAD antibody titres: high or moderate
3. **Cerebellar ataxia**
4. **Insulin-dependent diabetes mellitus (IDDM)**
   - Age spectrum: Childhood & adolescence
   - Anti-GAD antibody titres: low to moderate titre
5. **In association with**
   - Antibodies to tyrosine phosphatase IA-2
   - T-cell immunity
6. **Autoimmune polyendocrine syndrome II**

**Other antibodies associated with SPS**
- **Anti-Pancreatic islet cell** (60%)
  Also found in type I diabetes, although with lower titre and a different staining pattern
- **Anti-PCA2**

**Therapy**
*Unfortunately, treatment is rarely completely effective.*

**Symptomatic**
- **Diazepam** (very high doses; 20 mg to 300 mg/day)
- **Clonazepam**
- **Baclofen**
  - **Oral**: adjunct medication
  - **Pump** (intrathecal)
  - **Indication**: severe syndromes
  - **Warning**: acute withdrawal has been fatal

**Valproate**
**Tiagabine**: 6 mg qd

**Immunomodulatory therapies**
- **Corticosteroids**: high dose solumedrol with tapering
  - **Improvement over months**
- **Intravenous high-dose IgG**
- **Plasma exchange**
- **Rituximab**

---

**Stiff-person syndrome (SPS), variants**

The associated autoantibody is **Anti-GAD** in all the variant syndromes

**Table 8:**

<table>
<thead>
<tr>
<th>Enumeration</th>
<th>SSPS, variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Focal SPS</td>
</tr>
<tr>
<td>2</td>
<td>Jerking SPS</td>
</tr>
<tr>
<td>3</td>
<td>PERM</td>
</tr>
<tr>
<td>4</td>
<td>In PCD, also with anti-GAD</td>
</tr>
<tr>
<td>5</td>
<td>Other SPS</td>
</tr>
</tbody>
</table>

**1. Focal SPS**
Most frequently, this is a stiff-leg syndrome or alternatively, a stiff-arm syndrome.

**Onset** 35 to 60 years

**Clinical features**
**Stiffness and spasms** of lower limbs
Stimuli: especially voluntary movement; also reflex stimuli
- Asymmetric
- Posturing of feet
- Trunk spared

Treatment (partial benefit)
Baclofen, Diazepam

2. Jerking SPS
Clinical features
Stiffness: axial and lower limb
Later features
- Brainstem myoclonus
- Upper motor neuron signs
- PERM, see below

Progression over decade

3. Progressive encephalopathy with rigidity and reflex myoclonus (PERM)
Onset: subacute (weeks)
Clinical features
Stiffness
- Distal > proximal at disease onset
Rigidity
Spasms: episodic
Muscle wasting & weakness
Autonomic
- Hyperhidrosis associated with spasms
Cranial nerves
- EOM: nystagmus and ophthalmoplegia
- Blindness
- Deafness, dysarthria
Other CNS
- Long tract
- Vertigo
- Preserved intellect

Progression
- Over months and usually, death within one to 39 months
- Some cases remain mild

Investigations
Neurophysiology: similar to SPS and brainstem myoclonus
Serum: anti-GAD, anti-Glycine receptor
CSF: inflammatory

Pathology
- Perivascular inflammation
- Gliosis in spinal cord, pons and medulla
- Neuronal loss: spinal gray

4. SPS in cerebellar syndrome with anti-GAD
Epidemiology
Onset age: females 20 to 75 years

Clinical features
The onset is slowly progressive.
Ataxia: limb and trunk
Nystagmus
Dysarthria (50%)
Stiffness (15%)
No brainstem involvement

Associated disorders
- Late-onset insulin-dependent diabetes mellitus
- Thyroiditis
- Poly-endocrine syndrome

Additional antibodies
- Anti-Parietal cell

MRI: non-diagnostic.

Treatment: not described

5. Other paraneoplastic SPS
Suggestive features
SPS confined to upper limbs.

Rapid disease progression to fixed joint deformities

Also associated
- Sensory ganglionopathy

Neoplasms
- Breast
- Lung (small-cell)

Additional antibodies
- Anti-Amphiphysin

Treatment: Not described
Selected references


Paraneoplastic autonomic neuropathy (AAN)

Paraneoplastic autonomic neuropathy:
Paraneoplastic autonomic dysfunction of the ganglions and parasympathetic & sympathetic nerves which is associated with a variety of cancers and onconeural antibodies. This disorder is consistent with an IgG-mediated rather than T cell-mediated pathogenesis. [2]

1. Pandysautonomia
Autoimmune autonomic neuropathy (AAN) appears to fulfill the criteria of an antibody-mediated autoimmunity. This disorder has also been nicknamed "auto-nomic myasthenia gravis".

Clinical features
- Orthostatic hypotension without compensatory tachycardia
• Gastrointestinal dysmotility (80%)
• Anhidrosis (60%)
• Dry eyes and mouth
• Pupillary response reduced (30%)
• GU: urinary or erectile dysfunction (30%)
• Sensory paraesthesia in extremities (25%)
• Cough.

Investigations

CSF
• Elevated protein in 60%
• Typically, there are no cells

Antibody
• Anti AChR (alpha3-type)
The nicotinic α3-AChR is located at autonomic ganglions

This autoantibody may be a feature of other disorders:
• Isaacs’ syndrome (50%)
• Lambert-Eaton myasthenic syndrome (10%)
• Myasthenia gravis (a few patients)

See also autonomic features of the anti-Hu and anti-CV2 (CRMP5) syndromes: subacute sensory neuropathy (SSN), chronic gastrointestinal pseudo obstruction.

Associated neoplasms
• Thymoma
• SCLC
• Bladder
• Rectum

Differential diagnosis
➢ Multiple system atrophy (MSA) with predominant autonomic failure (former term: Shy-Drager syndrome)
➢ Anti-Peripherin seropositive neuropathy with endocrinopathy

Treatment
• Oncological therapy of associated neoplasm
• Intravenous high-dose IgG, early after onset or at progressing disability

2. The following syndromes may also exhibit autonomic dysfunction:
• Paraneoplastic cerebellar syndromes: with anti-PCA2 antibodies; with CV2 (CRMP5) antibodies
• Paraneoplastic sensory-motor neuropathy with anti-CV2 (CRMP5) antibodies
• Morvan’s fibrillary chorea
• Opsoclonus / myoclonus
• Stiff-person syndrome (SPS)
• SPS variants: other paraneoplastic SPS

Selected references
Paraneoplastic motor neuropathy

Paraneoplastic motor neuropathy:
Specific features please see also:
- Paraneoplastic motor neuron disease?
- Paraneoplastic sensory-motor neuropathy with anti-Hu antibodies
- Cerebellar syndromes with anti-PCA2 antibodies

Onset
After diagnosis of tumour

Course: progressive then stabilization or improvement

Epidemiology
Majority male & > 50 years

Clinical features
Weakness
- Asymmetric; arms > legs
- Mild and sometimes only lower motor neuron
- Normal bulbar

Cramps: painful
Painless in some patients

Associated neoplasms
- Non-Hodgkin Lymphoma
- Also other lymphomas & myeloproliferative disorders
- Ductal adenocarcinoma of breast

Investigations
- CSF: No cells; mildly increased protein
- MRI: Spinal cord normal
  ? Neuronopathy

Paraneoplastic sensory-motor neuropathy

Paraneoplastic sensory-motor neuropathy:
Using the currently available assays, onconeural antibodies are detectable in about 30% of patients with solid cancer and sensory-motor neuropathies. Mixed-type neuropathy is also an observation in malignant monoclonal gammopathies, associated with plasma cell malignancies (i.e. myeloma), B-cell leukaemias, and lymphomas.

Sensory-motor neuropathy
- Associated with anti-Hu or anti-CV2 antibodies and in some patients both autoantibodies
- Possibly, anti-Pyridoxal phosphatase
- Paraproteinaemic disorders

Clinical features

Electrophysiology
- Showing axonal and or demyelinating processes

Antibodies
- Anti-Hu seropositive patients

Sensory or motor neuropathy in about 15%-30% of these patients
- Subacute sensory neuronopathy (SSN)
- Motor symptoms usually resulting from motor neurone degeneration
- In about 30%, there is an equal proportion of sensory and motor involvement
- Frequently, the distribution is asymmetrical or multifocal

Note: Both mononeuritis multiplex and polyradiculopathy may resemble this disorder. Moreover, an acute severe evolution in the four limbs may mimic the Guillain-Barré syndrome.
Anti-CV2 seropositive patients

Polyneuropathy in about 60%
- Most frequently, this is a sensory-motor neuropathy preferentially affecting the lower limbs
- Pain is less frequent than with a finding of anti-Hu antibodies

Other features (in about 65%)
- Central nervous system disorder
- Autonomic neuropathy
- Eye involvement

Paraproteinaemias (monoclonal gammopathies)
- M-components (IgA, IgG, IgM)

Anti-Pyridoxal phosphatase may also be a finding

This autoantibody is a finding in sera of patients with lung cancer and well-differentiated thyroid cancer. They may also be a feature of an autoimmune thyroid disorder. Pyridoxal phosphatase is a co-enzyme of vitamin B6 (pyridoxine). Theoretically therefore, such antibodies may cause seizures and in particular a sensory-motor neuropathy with burning paraesthesias and eventually motor deficits. However, there are no reports about PNS related to anti-Pyridoxal, so such a disorder awaits discovery.

Please, also see
- Paraneoplastic cerebellar syndromes: CV2 (CRMP5) syndrome
- Opsoclonus / myoclonus: anti-Ri syndrome (due to other antibodies than anti-Ri)

Selected references
Paraneoplastic sensory neuronopathy (PSN, SSN)

Paraneoplastic sensory neuronopathy: This disorder is a classical PNS characterized by subacute and rapidly progressive neuropathy with pain, paraesthesia, and sensory loss. Most frequently, it is associated with SCLC and anti-Hu antibodies. The disorder is also called subacute sensory neuronopathy (SSN), since the lesions are primarily located to the nerve cell body (anti-Hu is a neuronuclear antibody, ANNA1), justifying the term neuronopathy. This disorder is also known as Denny-Brown’s syndrome. Cf. also PEM and PCD for more details about the anti-Hu syndrome.

Epidemiology
- **Males** in about 20-85% (US & European study, respectively). The difference may be attributable to varied smoking patterns.
- **Age of onset**
  - Mean 60’s (range 35-85 years of age)
- **Tobacco smoking**: > 95 %

Clinical features
**Painful paraesthesias and dysesthesias** (80%)
- Asymmetric, distal or proximal

**Sensory loss** (95%), all modalities are involved
- Proprioceptive loss: prominent
- Ataxia: sensory
- Pseudoathetosis

**Distribution**
- Proximal and distal
- Asymmetric (35%) or symmetric
- Upper limb only (25%)
- Lower limb only (45%)

**Motor**
- Normal (75%)
- Occasional sensory-motor involvement (25%), possibly subclinical
- The weakness may be proximal or distal
- In rare cases (5%), amyotrophy or fasciculations

**Course**
- Initial localized pain or sensory loss
- Then progression over days to six months
- Subsequently, plateau with little improvement
- Occasional improvement with treatment-induced remission of the neoplasm

Favourable PNS prognosis is associated with
- Variable survival data: similar to or better than in anti-Hu-seronegative patients
- Significant response, related to oncologic treatment
- Limited disease at time of diagnosis
- Initial metastases tend to spare nervous system

Less common outcomes
- Mild course
- Acute (< 24 hrs. in about 3%)
- Chronic (> six months in about 15-40%)

**Survival**: mean 28 months (6 months to 8 years)

**Associated syndromes** (40-70%)
- Limbic encephalitis ± seizures (10%)
- Epilepsy partialis continua
- Cerebellar: ataxia and nystagmus
- Brainstem encephalitis
- Vestibular disorders
- Oculomotor paresis
- Bulbar palsy
- Hearing loss
- **Myelitis**: patchy weakness with arms > legs
- **LEMS**
**Autonomic (30%)**
- Blood pressure: labile, hypotension (20%)
- Oesophageal achalasia
- Gastro-paresis
- Pseudo-obstruction
- Constipation (10%)
- Intestinal obstruction (10%)
- Urinary dysfunction (10%)
- IADHS (inappropriate ADH syndrome)
- Maybe primary lateral sclerosis (PLS)

Patients may also have a multifocal CNS disorder:
paraneoplastic encephalomyelitis (PEM), please see specific chapter.

**Associated neoplasms** (in 88%, and often small & slow growing)
- **Small-cell lung cancer**: strongest neoplasm association
  - **Frequency**: 80% of Hu positive serums
  - **Prevalence**: 17% of SCLC.
- **Others (rare)**
  - Breast, ovary, renal, testis, prostate, oesophagus, melanoma, thymoma, Hodgkin’s disease
  - These neoplasms may coexist with small-cell lung cancer

**Investigations**

**Note.** SCLC may escape the initial detection and only be disclosed upon follow-up testing (30%).

**MRI, PET.**

**Surgical examinations**
Bronchoscopy, mediastinoscopy, thoracotomy

**Electrodiagnostic**
Sensory nerve action potentials

**Pathology**
- Patchy dorsal root ganglion inflammation and neuronal loss
- About 50% with inflammation elsewhere in spinal cord or brain
- Spinal cord with loss of axons in posterior columns

- Diffusely absent or reduced.
- May be variable among nerves
*Motor studies show variable involvement*
- Often normal
- Occasionally, there is axonal loss, which may occur without associated weakness.

**CSF**
- **Cells**: in about 50%, the number of mononuclear cells is elevated (2 to 26/mm3).
- **Protein**: high (20 to 190) in 70%
- **Oligoclonal bands**

**Autoantibodies**
**IgG versus Hu (ANNA1).**
- **Cell targets**: selective staining of nuclei
  - Neurons (PNS & CNS), adrenohypophysis, adrenal cortex, retina

**Clinical correlations**
- **Low titres** are associated with neoplasm not provoking neurologic symptoms
- **High titres** are associated with neoplasm and SSN

**Antibody location**: serum and CSF

**Antibody type**
- All subtypes of IgG, although predominantly IgG1
- Hu antigens
- RNA binding proteins
  - Hu is a family of 35 to 40 kDa neuronal nuclear proteins. The proteins are HuD, HuC, Hel-N1, Hel-N2, ple21

**Other antibodies**
- **Anti-CV2 (CRMP5)** in about 15%
- **Serum M-protein**: not reported

- Intra-lesional lymphocytes of CD45RO-type (memory cells)

**Differential diagnosis**
Toxic: cis-platinum
Pyridoxine deficiency
Sjögren's syndrome
Treatment

Unfortunately, it is rare to observe any effect on the neurologic syndromes.

Oncologic

- Usually, the anti-Hu titre is reduced after tumour treatment.

Selected references

In contrast to the central and peripheral nervous system, the NMJ is not protected by any barrier, leaving it relatively unhindered exposed to toxins, chemical agents, and autoantibodies. The neuromuscular transmission is known in details (Figure 2), including the composition and function of many structures. Accordingly, much of the pathogenesis of NMJ disorders has been determined down to a molecular level. This knowledge has become the basis for a rational and quite often very successful therapy. Compared to the treatment of PNS at other locations, this is also true for the remedy of these syndromes at the NMJ.

**Figure 2:**
**Various structures and autoimmune disorders of the NMJ**

**Abbreviations:** AChR: acetylcholine receptor (nicotinic or muscarinic); TRPC3: transient receptor potential channel 3; MuSK: muscle specific tyrosine kinase receptor; RyR1: ryanodine receptor 1

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**The human neuromuscular junction:**

*A rectifier and fine tuned switch*
Lambert-Eaton myasthenic syndrome (LEMS)

Lambert-Eaton myasthenic syndrome:
An autoimmune presynaptic disorder of the NMJ, characterized by muscle weakness, autonomic features, and antibodies directed to the voltage-gated Ca-channel (VGCC) of P/Q-type and/or to the muscarinic AChR of M1-type. This disorder appears to fulfill the criteria of an antibody-mediated autoimmunity.

Clinical features
Muscle weakness
Typically, the chronology of the distribution of the weakness is the reverse of that of myasthenia gravis. In more than 90%, the weakness starts proximally in the legs. The paresis can then spread to other striated muscles in a caudo-cranial order. In some patients, this might lead to a need for artificial respiration. Ptosis and ophthalmoplegia can be present, but tend to be milder than in autoimmune myasthenia gravis.

Autonomic dysfunction
Dry mouth, dryness of the eyes, blurred vision, impotence, constipation, impaired sweating, or orthostatic hypotension. The autonomic dysfunction is mostly mild to moderate, in contrast to the severe disabling autonomic dysfunction in the anti-Hu syndrome.

Cerebellar degeneration
In rare cases, patients with LEMS and SCLC develop such features. In some patients, cerebellar degeneration is present together with anti-vg-Ca channel antibodies, but without clinical signs or symptoms of myasthenic muscle weakness.

Maybe it is related to anti-SOX1 (anti-Glial nuclear antibodies, AGNA), the target being the Bergman glia in the Purkinje cell layer.

See also: “Cerebellar syndromes with anti-PCA2 antibodies”.

Associated neoplasm
In more than 50 % LEMS cases small-cell lung cancer (SCLC) is co-existent, and most frequently found within two years after the diagnosis of LEMS.

Pro-GRP (gastrin-releasing peptide) and SOX1 antibodies both appear to be highly associated SCLC markers, also without a co-existent paraneoplastic syndrome.

Anti-SOX seropositivity is a feature of about 60% of SCLC cases with LEMS.

Table 9

<table>
<thead>
<tr>
<th>LEMS associated neoplasms</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary malignancies</td>
<td>79</td>
</tr>
<tr>
<td>(Small cell lung carcinoma)</td>
<td>67</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>4</td>
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<tr>
<td>Miscellaneous</td>
<td>11</td>
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<tr>
<td>Prostate carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Laryngeal carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Lymph metastasis, unknown primary</td>
<td>3</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Gall bladder carcinoma</td>
<td>0.7</td>
</tr>
<tr>
<td>Rectal adenocarcinoma</td>
<td>0.7</td>
</tr>
<tr>
<td>Carcinoma of maxillary glandule</td>
<td>0.7</td>
</tr>
<tr>
<td>Malignant thymoma</td>
<td>0.7</td>
</tr>
<tr>
<td>Ameloblastoma</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Diagnostic criteria
A typical history and clinical findings with in addition at least one of the following:
1. Low compound muscle action potential after nerve stimulation with decrement at low frequency stimulation (3 Hz) of more than 10%, and increment after high frequency stimulation (more than 20
Hz) or preferably maximal voluntary contraction) of more than 100%.

2. **Anti-vg-Ca channel (P/Q-type) antibodies**
   This is a finding in about 90% of the patients with no cancer; the frequency being 100% in SCLC cases with LEMS.

3. **Anti-AChR (muscarinic M1-type) antibodies** in about 80%
   These are directed to the presynaptic muscarinic AChR, which is associated with the TRPC3 channel (a transient receptor potential cation channel of subfamily C, member 3), and which is a Ca-influx channel. It appears that this autoantibody is a feature of all anti-vg-Ca channel seronegative LEMS patients.

**Anti-VGCC (N-type) antibodies**
These autoantibodies are a feature of LEMS sera in about 50% of the patients. Their role in the muscle weakness or autonomic dysfunction is unclear. They are not of significant value for diagnostic purposes.

**Anti-SOX1 (AGNA, anti-Glial nuclear antibodies)**
Autoantibodies against cerebellar Bergmann glia are a feature of LEMS sera in about 65% of the patients (sensitivity). Vice versa, SOX antibodies has a specificity of 95% to discriminate between LEMS with SCLC and non-tumour LEMS.

**Additional autoantibodies**
In cases with SCLC and symptoms other than muscle weakness
- Anti-Hu
- Anti-PCA2
- Anti-CV2
- Anti-Amphiphysin
- Anti-GAD
- Anti-Ri
- Anti-AChR (alpha3)
Please see the various syndromes associated with these autoantibodies.

**Small cell lung cancer**

**Treatment**

**Symptomatic**
- 3, 4-diaminopyridine, possibly combined with pyridostigmine

**Immunotherapy**
- Steroids
- Plasma exchange
- High-dose intravenous IgG
- Rituximab
- Azathioprine
- Cyclophosphamide

**Specific tumour treatment**
In SCLC local resection, radiotherapy, or chemotherapy may result in a remarkable recovery of the LEMS.
Selected references


Neuromyotonia, Isaacs' syndrome

Acquired neuromyotonia with peripheral nerve hyper-excitability

An autoimmune synaptic neuropathy characterized by intermittent or continuous widespread involuntary muscle contractions and autoantibodies directed to contactin-associated protein-2 (CASPR2) - the true target and being an accessory protein and integrated at vg-KC complexes.

The typical feature of this syndrome is continuous and quite pronounced muscle fibre activity, which is also present during sleep. The underlying mechanism is a severe instability of the terminal arborisations of motor nerves attributable to impaired function of the delayed rectifier $K^+$ channels that are ordinarily responsible for neuronal repolarisation following action potential firing. This disorder appears to fulfil the criteria of an antibody-mediated autoimmunity.

The milder cramp-fasciculation syndrome is neuromyotonia without fibrillations. There is also an overlap to Morvan’s syndrome. Moreover, see sporadic rippling muscle syndrome.
Onset
- With an onset, usually in late childhood or early adulthood, familial and acquired (primarily autoimmune) forms have been reported
- Most frequently < 60 years (mean 46 years)
- All origins: nine to 80 years

Differential diagnosis
- Paraneoplastic opsoclonus / myoclonus (POM)

Clinical features
The symptoms may fluctuate in severity over periods of months. Typically, exercise or muscle contractions are factors of precipitation.

Muscle twitching
Visible myokymia or neuromyotonia is symptomatic in 10 to 40%. The intermittent cramps and stiffness occur at rest, and may be induced or exacerbated by exercise. The predominant distribution of these features is distally in the arms and legs. Face, tongue and pharyngeal muscles may be involved. Moreover, an observation is delayed muscle relaxation and no percussion-induced contraction. The muscle activity continues during sleep.

Fatigue, hypertrophy
If existing, the weakness is absent or mild in about 30%, especially in overactive muscles. Muscle hypertrophy may occur in 20%. These features do not predict co-existence of MG or polyneuropathy.

Mental disturbances (25%)
Morvan’s syndrome, limbic encephalitis with personality change, insomnia, irritability

Other features
Sensory symptoms (30%), paraesthesias and numbness, hyperhidrosis (35% to 55%)
Tendon reflexes are often normal.

Voltage-gated-K⁺-channel

Course
Fluctuations, but no spontaneous remissions

Neurophysiology
EMG
Spontaneous axonal action potentials
In general, there is peripheral nerve hyperexcitability due to potentials arising along the course of motor axons and increased excitability of the nodal membrane. The potentials persist during general anaesthesia. NMJ blockade eliminates the abnormal muscle activity.

Distribution: limbs > trunk & face

Fasciculations may be the only sign of disease and may occur without myokymia. This may be clinically confused in the early stages with amyotrophic lateral sclerosis.

Myokymia
This feature is absent in some patients, and may develop on subsequent study, often as a mild continuous spontaneous activity.
These are spontaneous bursts of motor unit potentials of a brief duration, less than one second. They consist of two to five potentials per burst, with a frequency of 5-70 Hz. They recur regularly or irregularly (0.1 to 3 per second) and may persist after treatment.

**Neuromyotonia**

More persistent activity and muscle contraction. These are spontaneous bursts of single motor unit potentials, prolonged (several seconds) and of a frequency of 40 - 300 Hz. The bursts are very irregular and associated with persistent muscle contraction. Treatment may be able to reduce them. Another observation is repetitive F-waves.

**Associated neoplasms**

**Neoplasms**
- Lung
- Thymus
- Hodgkin’s disease

Isaacs’ syndrome often predates the diagnosis of these neoplasms.

**Associated disorders**
- Myasthenia gravis (seropositive, anti-AChR antibodies)
  The over activity begins with or after MG. The frequency of Isaac’s syndrome in myasthenics is estimated at about 10 to 20% and observed with a thymoma in patients > 40 years
- Penicillamine treatment
- CSF may occasionally show abnormality
  - Oligoclonal bands
  - Slightly increased protein

**Muscle biopsy**: fibre hypertrophy of type-I predominance

**Other disorders with K⁺-channel antibodies:**
- Cramp-fasciculation syndrome
- Limbic encephalitis
- Morvan’s fibrillary chorea
- KCNA1 mutations in episodic ataxia 1 (hereditary Isaacs-Mertens syndrome, myokymia 1)
- Morvan’s fibrillary chorea
- Polyneuropathy: sensory-motor with M-protein
- HIV infection
- Other associated immune disorders
  - Thyroid
  - Diabetes

**Investigations**

**Serum CK**: Elevated in 50%

**Autoantibodies**
- Anti-CASPR2 (contactin-associated protein-2) in more than 50% (Anti-voltage-gated K-channels)
  The targets are located at the dentate gyrus of hippocampus, at neural juxtaparanodes, and at the neuromuscular junction. In RIAs, using 2% digitonin extract of radio-labelled dendrotoxin, antibodies to Shaker types Kv1.1, 1.2, 1.6 are detectable, although not differentiated. Moreover, such VGKC extract are complexed with two other channel-complex proteins, leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis. Therefore, this assay is not specific to anti-VGPC.

- Anti-AChR (autonomic alpha3-type, 50%)
- Anti-AChR (adult-type, foetal-type), in co-existing paraneoplastic MG

**Nerve conduction studies** are usually normal.

**Treatment**

**Symptomatic**
- Carbamazepine (200 to 600 mg/day)
- Phenytoin (200 to 400 mg/day)
- Mexiletine

**Immunosuppression**
- Plasma exchange (short-term benefit).
- Prednisone
Selected references


Paraneoplastic seropositive myasthenia gravis with thymoma

Paraneoplastic seropositive* myasthenia gravis (SPMG with a thymoma):
An autoimmune postsynaptic disorder of the neuromuscular junction, characterized by the co-occurrence of a thymoma, myasthenic muscle weakness and autoantibodies directed to the acetylcholine receptor (AChR) in 100%, and in about 75% also by additional antibodies to other structures of the striated muscle cells (titin and the ryanodine 1 receptor). In contrast to the co-existent myopathy, the myasthenic part of the disorder fulfils the criteria of an antibody-mediated autoimmunity. See also myasthenia-gravis-associated myopathy and sporadic rippling muscle syndrome.

(*Seropositive = anti-AChR antibodies seropositive)

Thymomas vs. autoimmunity
The normal job of the thymus is to educate and export T-cells to the rest of the body, in order to help B-cells to make antibodies and stimulate other cells to protect against infections and neoplasms.

Unfortunately, the emergence of a thymoma often results in a vast excess of harmful T-cells, provoking various autoimmune disorders. It appears that a ‘dangerous’ tumour microenvironment is created with both pre-activation and antibodies to cytokines (IF-alpha, IL-12). Normally, AChRs of embryonic (foetal)-type are a feature of myoid cells of the thymus, very much in contrast to Titin and RyR1 epitopes. Unfortunately, these latter epitopes are characteristics of thymomas (cortical type?). Presumably, this neoplasm therefore provokes a synthesis of such autoantibodies and maybe to other targets as well under such conditions.

SPMG is co-existent in about 50% of patients with a thymoma. Otherwise, this neoplasm is associated with a variety of other autoimmune disorders and corresponding autoantibodies.

Frequently, thymoma patients are diagnosed with more than one such disorder.

Unrelated to a thymoma, MG is in itself associated with other antibodies, apart from maybe ANA
- Anti-Lymphocyte (60%)
- Anti-Nuclear (ANA, 30%)
- Anti-Thyroid (microsomal & thyroglobulin), 30%
- Rheumatoid factor (25%)
- Anti-Platelet (25%)
- Anti-Parietal cell (15%)
- Anti-Smooth muscle (10%)
- Coomb’s (10%)
Epidemiology in MG
The frequency of this neoplasm is about 10% of all myasthenics. The peak age at onset of thymoma-SPMG is in-between early- and late-onset MG (dichotomy by 50 years of age). For more details, see the adjacent figure.

Clinical features
- In general, a thymoma predicts more severe MG. Likewise, anti-Titin and anti-RyR1 antibodies are markers of a more severe course of the disorder.
- In paraneoplastic MG (thymoma), a frequent finding is severe weakness of the extraocular muscles. This is explicable in terms of the multiply innervated fibres at this location expressing embryonic (foetal) AChR at their NMJs.
- From the present evidence, one should also regard thymoma MG-patients as a group at special risk of myocardial pathology. Accordingly, should heart symptoms occur in such patients, consider the possibility of myocarditis (or pericarditis) related to MG and autoimmunity. Routinely however, and using the currently available modalities of heart examinations, it appears that regardless of any thymic pathology, MG patients should not undergo such examinations [16].

Investigations
Autoantibodies
If only MG symptoms are present, then primarily
- Anti-AChR (adult- & foetal-type)
- Anti-Titin (must be determined with an assay using the main immunogenic region (MIR))
  - Almost all MG patients with anti-titin and onset < 50 years of age have a co-existent thymoma, the exception being acute severe generalised MG
  - MG without thymoma: anti-titin in 50% to 90% of MG with age at onset > 50 years and not a feature of early-onset MG, see above.
- Anti-MuSK (a few case histories)
  - and anti-AChR seronegative

Please note that apart from anti-MuSK seropositive cases, thymomas are not encountered in anti-AChR antibody seronegative MG. Moreover, autoantibodies to various epitopes of striated muscles are associated with co-existent myopathy adding to the myasthenic weakness.

Secondary
If in addition to anti-AChR, anti-Titin is not a finding, then consider
- Anti-Striated muscle (unspecific) or anti-RyR1
  - Frequency in MG + thymoma: 80% to 90%
  - MG without thymoma: rare < 10%
• Positive also in MG with myositis

- **Anti-CASPR2** (formerly called anti-vg-K-channels)
  These channels are located at the neuromuscular junction and in the CNS, and Kv1.4 are also located in the heart & smooth and striated muscles

**Cytokine antibodies**
- Anti-IF alpha (interferon alpha) (75%)
- Anti-Il12 (interleukin 12)
  Autoantibodies against such “messenger molecules” are more common in MG patients with a thymoma than in those without (75% versus 30%). Typically, the titres of these autoantibodies increase substantially if a thymoma recurs after surgery. Accordingly, these antibodies are also valuable in the post-surgery monitoring of these patients.

**Titin, also known as connectin**
This giant muscle molecule is a molecular spring

**Ryanodine 1 receptor (RyR1)**
A major cellular mediator of Ca++-release in striated muscle

**In cases with findings other than strict myasthenic weakness, then also:**
- Anti-GAD
- Anti-CV2
- Anti-vg-Ca channel (P/Q-type)
- Anti-AChR (nicotinic alpha3, autonomic, ganglionic)
  Please see the various syndromes associated with these autoantibodies.

**Other investigations**
Follow the general guidelines for MG and search for a thymoma in anti-AChR seropositive cases. If striated muscle autoantibodies of any specificity are a feature as well, then the likelihood of a coexisting thymoma is much greater, but the non-finding does not rule out that anyhow, such a neoplasm may be present. If furthermore, anti-Cytokine antibodies are present, then the search for a thymoma should be intensive.

Somewhat puzzling, thymomas may be encountered up to several months or years before the onset of MG, at about the time of the MG diagnosis, and subsequently also up to several years hereafter. Therefore, a non-thymoma SPMG diagnosis may necessitate repeated search for this neoplasm at suitable intervals, in particular in cases with a later onset than before 30 years of age.

**Treatment**
Follow the general principles in MG.
In addition
- Drug to enhance RYR-related sarcoplasmic Ca++-release

**Immunosuppression**
Compared to SPMG without a thymoma, paraneoplastic SPMG is more aggressive and often requiring
- Early and more intensive combined immunosuppressive therapy with steroids and azathioprine
- A series of plasma exchanges or alternatively, intravenous high-dose IgG in order to adequately manage MG crises
**Surgery**
Removal of the thymoma is an option upon oncologic indications only, since it is likely that the myasthenic disorder in itself will substantially deteriorate soon after the surgical procedure, possibly rendering more intensive immunosuppressant control necessary for up to several years subsequent to operation.\(^2\)

**Risk of passive transfer MG**

**Comprises**

- **Neonatal MG**
- **Acquired arthrogryposis multiplex**

The chapter: “Maternal autoantibodies and passive transfer in humans” provides a detailed review of this.

The possibility of passive transfer MG is of great concern in a myasthenic woman planning a pregnancy or already being so. Note however, that even though a fertile thymoma patient does not show any myasthenic signs, the foetus may still be at risk, since – in such a case, anti-AChR to the embryonic receptor may be present in the serum of the woman, not causing her any harm, but being detrimental to neuromuscular transmission of a foetus.

Among thymoma-MG patients, the relative difference in titres between the two specificities of anti-AChR antibodies may vary substantially. This has implications to the risk of transferring MG to an offspring.

**In short:**
Whether a female thymoma patient is diagnosed with MG or not, in relation to a pregnancy consider examination of a serum sample:

- **Anti-AChR antibodies**, preferably by using an assay with a mixture of adult- and foetal-type human receptor from different cell lines in a standardised ratio
  - A ratio of foetal- vs. adult-type autoantibodies may provide a more useful estimate of the actual risk, since such a calculation results in more emphasis of fraction of antibodies to the gamma subunit.

- **Monitor such a pregnancy carefully**
  - Longitudinal measurements of anti-AChR
  - Decreased foetal movements
  - Signs of hydramnios

- **Treatment during pregnancy**
  - Upon rising titres or ominous signs, consider more intensive treatment bearing in mind that this must serve to decrease the concentration of antibodies.
  - Cf. also the chapter “General therapeutic considerations”.
  - If plasma exchange by any technique is the choice, then take extra care to avoid drastic shifts in hormone levels, since this may result in an unwanted abortion.

**Selected references**


Paraneoplastic myopathies

In association with a variety of neoplasms, the features of these myopathies are a predominantly proximal and symmetrical muscular weakness, and maybe arthralgias, dermatologic manifestations or myasthenic fatigue.

Table 10: Some currently known disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Autoimmune myopathy</th>
<th>Associated autoantigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Dermatomyositis</td>
<td>Mi2β, SAE2, SAE1, M2α, TIF1γ, PX2</td>
</tr>
<tr>
<td></td>
<td>Polymyositis</td>
<td>SRP, Jo-1, PL-12, PL-7, EJ, OJ</td>
</tr>
<tr>
<td></td>
<td>Overlap</td>
<td>PM-Scl75, PM-Scl10, KU</td>
</tr>
<tr>
<td>B</td>
<td>Acute necrotizing myopathy</td>
<td>HMGCRC</td>
</tr>
<tr>
<td>C</td>
<td>Inclusion body myositis</td>
<td>cN1A (Mup44)</td>
</tr>
<tr>
<td></td>
<td>Severe autoimmune myopathy (IIM)</td>
<td>FHL1</td>
</tr>
<tr>
<td>D</td>
<td>Paraneoplastic myasthenia gravis associated myopathy</td>
<td>Titin</td>
</tr>
<tr>
<td>E</td>
<td>Sporadic rippling muscle syndrome</td>
<td>Titin isoform N2A, ATP synthase 6, PPP1R3</td>
</tr>
</tbody>
</table>

Other

- Giant cell myositis
- Eosinophilic myositis
- Granulomatous myositis
- Macrophagic myofasciitis
- Pipestem capillary disease
- Myositis related to other connective tissue diseases

A. Polymyositis, dermatomyositis

Poly- or dermatomyositis is an idiopathic inflammatory myopathy without or with characteristic cutaneous manifestations. The incidence of polymyositis and dermatomyositis is 5-10 cases per 100,000 individuals.

Polymyositis is presumed to be an autoimmune-mediated disease secondary to defective cellular immunity, which may be due to diverse causes that may occur alone or in association with viral infections, malignancies, or connective-tissue disorders. Evidence suggests that a T-cell-mediated cytotoxic process is directed against unidentified muscle antigens.

Onset
- Adults over 30 years of age; female-to-male ratio 2:1
- Slowly progressive over weeks to months; active 2-3 years

Dermatomyositis is likely the result of a humoral attack on the muscle capillaries and small arterioles. Complement c5b-9 membrane-attack complex is deposited and is needed in preparing the cell for destruction in antibody-mediated disease. B-cells and CD4 (helper) cells are also present in abundance in the inflammatory reaction associated with the blood vessels.

Clinical features

Myopathy
- Muscular weakness, primarily proximal and most often symmetrical

Skin manifestations
- Heliotrope rash involving the periorbital skin
- Photosensitive poikilodermatous eruption
- Erythematous scaly plaques on dorsal hands with periangual telangiectasia and joint eruptions (Gottron papules)
Diagnosis
The following combination:
- Typical skin changes
- Muscle weakness
- Elevated serum creatinine kinase
- Characteristic neurophysiologic findings
- Muscle biopsy

Remarks
- Typically, cancer is a finding simultaneously with the myopathy diagnosis
- In dermatomyositis, a neoplasm is found more frequently in women than in men

Associated neoplasms
- Ovarian
- Lung
- Pancreatic
- Stomach
- Colorectal
- Non-Hodgkin lymphoma

Table: Association with malignant disease

<table>
<thead>
<tr>
<th>Dermatomyositis</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.0</td>
<td>2.5-3.6</td>
</tr>
<tr>
<td>Ovarian</td>
<td>10.5</td>
<td>6.1-18.1</td>
</tr>
<tr>
<td>Lung</td>
<td>5.9</td>
<td>3.7-9.2</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>3.8</td>
<td>1.6-9.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.5</td>
<td>1.7-7.3</td>
</tr>
<tr>
<td>Colorectal</td>
<td>2.5</td>
<td>1.4-4.4</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3.6</td>
<td>1.2-11.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polymyositis</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3.7</td>
<td>1.7-8.2</td>
</tr>
<tr>
<td>Lung</td>
<td>2.8</td>
<td>1.8-4.4</td>
</tr>
<tr>
<td>Bladder cancers</td>
<td>2.4</td>
<td>1.3-4.7</td>
</tr>
</tbody>
</table>

Hill CL et al. 2001 - 618 cases of dermatomyositis, of whom 198 (32 %) had cancer: 115 of the 198 (58 %) developed cancer after diagnosis of dermatomyositis. 137 of the 914 (15 %) cases of polymyositis had cancer, which developed after diagnosis of polymyositis in 95.

Laboratory markers
- Antinuclear antibody (ANA) is frequently positive.

Irrespective of neoplasms, there is association also with these autoantibodies:

1. Myositis-specific antibodies (MSA)
   - Jo-1 (25% seropositivity in myositis)
   - Mi-2 (25% seropositivity in dermatomyositis)
   - PL-7, PL-12
   - EJ, OJ
   - SRP
   - Ku
   - (KS, KJ, PMS1)

2. Myositis-overlap antibodies
   - PM-Scl 75, PM-Scl 100
   - Ro-52
   - (U1-nRNP 70 k, U1-nRNP A, U1-nRNP C)

Anti-SRP is associated with an aggressive course of polymyositis and unsatisfactory effect of treatment.
**Anti-synthetase syndrome**

<table>
<thead>
<tr>
<th>Symptomatology</th>
<th>Autoantigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>polymyositis</td>
<td>Jo-1, EJ, OJ, PL-7, PL-12</td>
</tr>
<tr>
<td>fever</td>
<td></td>
</tr>
<tr>
<td>polyarthritis</td>
<td></td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td></td>
</tr>
<tr>
<td>interstitial lung disease</td>
<td></td>
</tr>
</tbody>
</table>

3. **Anti-TIF1γ, anti-MDAS, anti-NXP2**

<table>
<thead>
<tr>
<th>Anti-TIF1γ (transcriptional intermediary factor 1-gamma) – alias anti-155/140</th>
<th>Cancer associated DM</th>
<th>Classical DM</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58 % (n=12)</td>
<td>5 % (n=39)</td>
<td>0 % (n=20)</td>
</tr>
</tbody>
</table>

**Anti-MDAS** (melanoma differentiation-associated gene 5)
All such seropositives (26 %, n= 82) had DM

Hashino et al.. *Rheumatology 2010; 49 (9): 1726-36*

**Anti-NXP2 (MORC3) or anti-TIF1γ**

Cancer associated DM: 83 % (n=213)


**Treatment**

**Oncologic & immunosuppressants**
- Corticosteroids
- Azathioprine
- Intravenous administration of high-dose IgG

**B. Necrotizing myopathy**

This autoimmune disorder may represent a severe form of polymyositis.

**Onset**
- Quite rare disorder
- Rapid progression over one to three months

**Clinical features**
- Symmetrical and predominantly proximal weakness
- May also include dysphagia (60 %)
- Arthragias (50 %)
- Eventually, severe functional disability

**Associated neoplasms (13 %)**
- Lung
- Bladder
- Breast
- Gastrointestinal tract

**Investigations**

**Serum creatine kinase**
- Markedly elevated

**Neurophysiology**
- Evident myopathic findings

**Muscle biopsy**
- Patchy necrosis and perimysial phosphatase staining with little inflammation

**Tissue type**
- Increased frequency of HLA-DR11 (70-90 % vs. about 20 % in controls)
- **Protective**: DQA1; DQB6

**Associated antibody**
- **Anti-HMGCR** (3-hydroxy-3-methylglutaryl-coenzyme A reductase) - the rate-limiting enzyme for cholesterol synthesis. Serum from such patients specifically recognizes the intracellular catalytic domain of HMGCR.
Differential-diagnoses
- Statin-provoked rhabdomyolysis
Interestingly, it appears that the frequencies of statin use differ in anti-HMGCR seropositives versus dermatomyositis and polymyositis cases (83 %, 25 % and 37 %, respectively) – and using the chi²-test, this is significant.

Statins may cause diffuse or multifocal up-regulation of MHC-I expression even in non-necrotic fibres.

Statins are among the most commonly prescribed medications that significantly reduce cardiovascular risk in selected individuals. However, these drugs can also be associated with muscle symptoms ranging from mild myalgias to severe rhabdomyolysis.

While statin myotoxicity is usually self-limited, in some instances statin-exposed subjects can develop an autoimmune myopathy typically characterized by progressive weakness, muscle enzyme elevations, a necrotizing myopathy on muscle biopsy, and autoantibodies that recognize HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase), the pharmacologic target of statins.

These antibodies are also found in some autoimmune myopathy patients without statin exposure. Importantly, anti-HMGCR antibodies are not found in the vast majority of statin-exposed subjects without autoimmune myopathy, including those with self-limited statin intolerance.

Thus, testing for these antibodies may help differentiate those with self-limited statin myopathy who recover after statin discontinuation from those with a progressive statin-associated autoimmune myopathy who typically require immune-suppressive therapy.

Treatment
Oncologic and immunosuppressants
- Corticosteroids
- Azathioprine
- Intravenous administration of high-dose IgG

C. Inclusion body myositis, sporadic

This myopathy is associated with anti-cN1A (anti-Mup44) and rarely endometrial carcinoma of the uterus; please see below.

Onset and incidence
This sporadic form of IBM (sIBM) is an age-related disease – a type of muscular dystrophy; and the most frequent acquired myopathy seen in adults aged over 50 years.

The mean age of onset is around 60 years (but with considerable variation). About 20% of cases display symptoms before 50. It appears to be slightly more common in men. Prevalence is about 15 per million in the overall population, with a prevalence of 50 per million population in people over 50 years of age.

Hereditary - hIBM:
1. IBM1 is listed under OMIM 601419: MYOPATHY, MYOFIBRILLAR, 1; MFM1
2. IBM2 is listed under OMIM # 600737. INCLUSION BODY MYOPATHY 2, AUTOSOMAL RECESSIVE; IBM2
3. Another form of IBM2 is Nonaka distal myopathy; see: OMIM # 605820: NONAKA MYOPATHY; NM
4. IBM associated with Paget disease of bone and dementia (IBMPFD; see: OMIM # 167320 INCLUSION BODY MYOPATHY WITH EARLY-ONSET PAGET DISEASE AND FRONTOTEMPORAL DEMENTIA; IBMPFD
Clinical features
Since s-IBM is an acquired myopathic process, weakness or impairment of muscle function in the area(s) affected is the presenting symptom. The disease follows a slowly progressive course.

- The distribution of weakness in s-IBM is variable, but both proximal and distal muscles are usually affected and, unlike polymyositis and dermatomyositis, asymmetry is common.
- Early involvement of the knee extensors, ankle dorsiflexors, and wrist/finger flexors is characteristic of s-IBM.
- Weakness of the wrist and finger flexors is often disproportionate to that of their extensor counterparts. Hence, loss of finger dexterity and grip strength may be a presenting or prominent symptom.
- Dysphagia is common, occurring in 40-66% of patients with well-established disease and in 9% of patients at presentation. Dysphagia may manifest as a feeling of stasis, a need to swallow repeatedly, regurgitation, or choking. Mild facial weakness may be a feature in about one third of patients.
- Isolated erector spinae weakness or “droopy neck” syndrome has been reported with s-IBM.
- Myalgias and cramping are relatively uncommon.
- Sensory and autonomic dysfunction is not present except in patients with a concurrent polyneuropathy.
- Cardiac disease is common; it is most likely due to the older age of most patients. Direct cardiac muscle involvement by the disease has not been demonstrated.

Associated neoplasms
Uterus: endometrial carcinoma

Differential-diagnosis
Polymyositis, motor neuron disease, myasthenia gravis

Investigations
In most cases of s-IBM, serum CK level is normal or elevated to a mild-to-moderate degree. Elevation greater than 12 times normal may occur but is rare.

Neurophysiology
Electromyography studies usually display abnormalities

Muscle biopsy
May display several common findings including; inflammatory cells invading muscle cells, vacuolar degeneration, inclusions or plaques of abnormal proteins. sIBM is a challenge to the pathologist and even with a biopsy, diagnosis can be ambiguous

Associated antibodies
- Anti-cN1A (Cytosolic 5'-nucleotidase 1A) – alias anti-Mup44
- Anti-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase)

Treatment
Consider immunosuppressant or myofibre regenerator
- Alemtuzumab
- Bimagrumab
The FDA have granted breakthrough status for bimagrumab (stimulating myofibre regeneration) based on the results of a phase 2 proof-of-concept study that showed that the drug substantially benefited patients with sIBM compared to placebo

Severe dysphagia may require cricopharyngeal myotomy or placement of a gastrostomy tube. Chemodenervation with botulinum toxin A injection into the upper esophageal sphincter has also been shown to be of benefit.
This myopathy is associated with postsynaptic disorders of the NMJ, comprising:
- Paraneoplastic-SPMG (thymoma)
- Late-onset SPMG

**Abbreviations:** SP is anti-AChR seropositive; MG is myasthenia gravis.

Provocation appears to be a common denominator in both disorders: either by a neoplasm or by environmental factors.

**Onset**
See figure showing the annual incidence rates of early-, late-onset & thymoma-MG in the section “Paraneoplastic SPMG with thymoma”.

**Clinical features**
- Symmetrical and predominantly proximal weakness
- Myasthenic fatigue
- Muscular atrophy
  - More or less severe muscular atrophy is a common feature in all these cases, combined with the finding of anti-Titin and other anti-striated antibodies.

**Comments**
SPMG fulfils the criteria of an autoantibody-mediated disorder. Since the anti-Striated muscle antibodies are for intracellular structures, it is tempting to speculate that the myopathic component may be T-cell mediated.

**Neurophysiology**
- **Myopathic findings**
  - In more than 20% of thymoma-MG
  - In more than 30% of late-onset MG

**Associated neoplasm**
- **Thymoma:** a finding in about 10-15% of all MG cases

**Associated antibodies**
- **Anti-AChR** (100%, adult- and foetal-type)
- **Anti-Titin:** the presence of these antibodies correlates with myopathy per se and with the overall clinical severity of the disorder.
  - 70% in thymoma-MG
  - 55% in late-onset non-thymoma MG
- **Anti-RyR1**
  - **Anti-Striated muscle (by immunohistochemistry):**
    - This unspecific method detects antibodies to various muscle epitopes, *for example* also the ryanodine receptor.
    - Accordingly, the frequency of seropositives is higher than compared with anti-Titin results.

**Treatment**
*Please see paraneoplastic MG.*
<table>
<thead>
<tr>
<th>Reference</th>
<th>Frequency of cancer (%)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigurgeirsson et al. 1992</td>
<td>61/392 (16 %)</td>
<td>Female 3.4</td>
</tr>
<tr>
<td></td>
<td>42/396 (11 %)</td>
<td>Male 2.4</td>
</tr>
<tr>
<td>Airio et al. 1995</td>
<td>31/203 (15 %)</td>
<td>Female 1.7</td>
</tr>
<tr>
<td></td>
<td>26/336 (8 %)</td>
<td>Male 1.8</td>
</tr>
<tr>
<td>Chow et al. 1995</td>
<td>19/71 (27 %)</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>12/175 (7 %)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Malignancy in myositis - Waimann et al. 2011**

**Cancer diagnosis**

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>DM (n=58)</th>
<th>PM (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>Lung</td>
<td>17%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Adenocarcinoma was the predominant histological type (DM 60%, PM 39%).

**Cancer diagnosis before onset**: PM 57%; DM 26%.

Overall, PM or DM were concurrent with cancer diagnosis or recurrence in 40% of the cases.
E. Rippling muscle syndrome, sporadic – autoimmune

This myopathy appears to be attributable to mechanical sensitivity and instability due an effect of anti-Striated muscle antibodies.

Onset
30 to 55 years

Clinical features
- Rippling muscles
- Rolling muscle contractions
- Muscle stiffness
- Myotonia
- Cramps
  - Induced by exercise or touching muscle

- Spread in transverse direction across muscle
- May be painful
- Distribution: cranial, proximal, distal
- Bulbar: dysphagia and dysarthria
- Normal sensation and tendon reflexes

Investigations
- Serum CK: mildly elevated
- Muscle biopsy: inflammation, lymphocytic
- EMG: normal with silent cramps

Antibodies
- Anti-Skeletal muscle (see below for specificity): use unspecific immunohistochemical methods to detect these antibodies, unless a specific method is available
There are three associated and distinct muscle antigens:

1. **Titin isofrom N2A**: Accordingly and as opposed to classical myasthenia gravis - in rippling muscle syndrome, the immunogenic region of titin is distinct from the main immunogenic region (MIR).

2. **ATP synthase 6**

3. **PP1R3** (protein phosphatase 1 regulatory subunit 3)

- **Anti-AChR** (alpha3-type and adult-type)

Although the mechanism of antibody penetration is not known, previous studies have shown that the autoantibodies in RMS can affect the contractile machinery of myofibres resulting in mechanical sensitivity and instability.

### Associated neoplasm

#### Selected references


### Associated disorders

- **Thymoma**

### Rule out

- **Hereditary rippling muscle syndromes**
  - dominant or recessive (genes RMD1 and CAV3)
  - quite similar features to those of the sporadic disorder

### Treatment

**Immunosuppression:** Prednisone or Azathioprine

**Benefit** appears to set in over 2 to 4 months

**Note:** Pyridostigmine may exacerbate this disorder.


42. Waimann CA, Olejeme KA, Tayar, JH, Lei X,Suarez-Almazor ME. Cancer Associated Myositis: Temporal Relationship, Survival and Risk of Cancer Recurrence. Results From A Large Historical Cohort in United States of America. *Arthritis & Rheumatism 2011 - Abstract*


Symptomatic overview

Paraneoplastic ataxia

Paraneoplastic ataxia:
For specific features, please see the following:
- Paraneoplastic cerebellar degeneration (PCD), including a comprehensive Table
- Paraneoplastic encephalomyelitis (PEM)
- Paraneoplastic opsoclonus/myoclonus (POM): in adults, anti-Ri syndrome

Paraneoplastic epilepsy

Paraneoplastic epilepsy:
For specific features, please see the following:
- Paraneoplastic limbic encephalitis (PLE)
- Paraneoplastic sensory neuropathy (SSN, PSN)
- Morvan’s fibrillary chorea
- Opsoclonus / myoclonus: adults
- Opsoclonus / myoclonus: Ri (ANNA2, NOVA1) syndrome
- Stiff-person syndrome (SPS)

Autoimmune encephalitis and epileptic seizures

In summary: recent studies in the field of paraneoplastic syndromes and autoimmune encephalitides provide several clues that suggest the immune aetiology of some types of epileptic disorders, including the acute presentation of symptoms, the frequent detection of CSF pleocytosis and oligoclonal bands in the context of negative viral studies, and the detection of CSF antibodies reacting with the neuropil of hippocampus and the cell surface of neurons.

These disorders can be divided into limbic and cortical extralimbic encephalitides and may have paraneoplastic or non-paraneoplastic aetiology.

Paraneoplastic autoimmune encephalitis with epilepsy

The associated antibodies include

<table>
<thead>
<tr>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu</td>
</tr>
<tr>
<td>Anti-CV2 (CRMP5)</td>
</tr>
<tr>
<td>Anti-Ta (Ma2)</td>
</tr>
<tr>
<td>Anti-Ri</td>
</tr>
<tr>
<td>Anti-Amphiphysin</td>
</tr>
</tbody>
</table>

While there is strong evidence that the first four immune responses are mediated by cytotoxic T-cells responses, there are studies indicating that amphiphysin antibodies may be directly pathogenic. Of these five immune responses, the anti-Hu antibodies are those most frequently described with seizures, epilepsia partialis continua, and status epilepticus. The underlying tumours are small-cell lung cancer (all antibodies), breast cancer (anti-Ri), germ-cell tumours of the testis (Ta/Ma2), and thymoma (CV2/CRMP5). With the exception of the encephalitis associated with
Ta/Ma2 antibodies, in which approximately 30% of patients respond to tumour removal and immunotherapy, the other disorders are rarely treatment-responsive.

Autoimmune encephalitides that are not strictly paraneoplastic

In a context of autoimmune encephalitides, there is an expanding group of that may occur with or without tumour association, depending on the type of antibody. A frequent feature of these immune responses (except for GAD antibodies and anti-ENO1) is that the autoantigens are extracellular and therefore accessible to circulating antibodies. These antigens include the excitatory glutamatergic receptors (NMDA, AMPA), the inhibitory GABA (B) receptor (GABBR1), and the recently reported true target antigens (LG11 and CASPR2) of antibodies previously attributed to voltage-gated potassium channels (VGKC). GAD antibodies usually associate with non-paraneoplastic stiff-person syndrome and cerebellar dysfunction, but there are increasing number of reports showing that these antibodies also occur with subtypes of limbic encephalitis and refractory epilepsy. Antibodies to the NR1 subunit of the NMDAR associate with a characteristic syndrome that presents with behavioural change or psychosis and usually progresses to a decline of the level of consciousness, catatonia, seizures, dyskinesias, autonomic instability, and frequent hypoventilation. AMPA receptor and GABA(B) receptor antibodies associate with a clinical picture of limbic encephalitis, with early and prominent seizures in the case of GABA(B) receptor antibodies. Recent reports indicate that LG11, a secreted neuronal protein, is the target antigen of limbic encephalitis previously attributed to VGKC. Interestingly, this disorder associates with frequent seizures (~80% of the patients) along with hyponatraemia. Moreover, mutations of LG11 are the cause of autosomal dominant partial epilepsy with auditory features (ADPEAF), also called autosomal dominant lateral temporal lobe epilepsy. In contrast, CASPR2, a protein that is expressed in brain and peripheral nerve, clustering the VGKC at the juxtaparanodal regions of myelinated axons is the target antigen of encephalitis and peripheral nerve hyperexcitability that may result in Morvan’s syndrome.

Anti-D1, anti-D2, anti-lyso-GM1 are findings related to the post-streptococcal neurological syndrome.

Anti-Alpha-enolase (ENO1) is associated with Hashimoto’s encephalitis and autoimmune thyroiditis.

**Prompt recognition of all the disorders associated with antibodies against cell surface antigens is important**

- They may also affect children and young adults (typical of anti-NMDAR encephalitis)
- They are responsive to immunotherapy and/or treatment of the tumour when appropriate

As a contrast, anti-GAD associated encephalitis is less treatment-responsive
**Paraneoplastic extrapyramidal disorders**

- Paraneoplastic extrapyramidal disorders:
  - For specific features, please see the following:
    - Paraneoplastic brainstem encephalitis (as a part of PEM)
    - Paraneoplastic cerebellar syndrome: anti-CV2/CRMP5 syndrome
    - Paraneoplastic choreo-athetosis (anti-CV2/CRMP5, anti-Hu)
    - Stiff-person syndrome (SPS)
    - Stiff-person syndrome, variants: suggestive features

**Paraneoplastic pain**

- Paraneoplastic pain
  - For specific features, please see the following:
    - Stiff-person syndrome (SPS)
    - Paraneoplastic sensory neuronopathy (SSN, PSN)
    - Paraneoplastic sensory-motor neuropathy
Maternal autoantibodies and passive transfer in humans

Reports of vertical transmission of cancer are exceptionally rare, although maternal cells do reach the foetus and cancer occurs in nearly one in 1000 pregnant women. Malignant melanoma is the best-known example of a cancer that can metastasize to the foetus. Another example is transfer to the foetus of an aggressive natural-killer-cell lymphoma in the mother, with fatal consequences to the infant.

It is conceivable that T-cell-mediated autoimmunity is transferable, since maternal cells may be a feature of the umbilical cord bloodstream. In theory, all autoimmune disorders, fulfilling the criteria of being antibody-mediated (Table 1), may also occur because of passive transfer from a mother to an unborn child, possibly leading to foetal or neonatal disorders. Another mechanism may be that neoplasms express antigens that are cross-reacting exclusively with structures of the foetus and that later on are replaced by adult ones (for example AChRs of the embryonic- and adult-types). In such cases, provoked antibodies may be beneficial to the mother and be potentially detrimental to the offspring.

Either such transferred PNS may resemble those of the mother or they may differ quite substantially (Table 8), since the infant is under development. Moreover, the severity of such a disorder may vary from transient neonatal ones, often both self-limiting and self-repairing, over various malformations, and maybe even to severe and permanent defects of the nervous system. The worst-case scenario is fatalities. Moreover, women beyond the normal age of fertility or having recovered from a cancer are increasingly seeking medical assistance to become pregnant.

Table 11: Foetal exposure to maternal autoantibodies

<table>
<thead>
<tr>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PNS resembling that of the mother</td>
</tr>
<tr>
<td>• Neonatal MG</td>
</tr>
<tr>
<td>2 Deformities</td>
</tr>
<tr>
<td>• Acquired arthrogryposis multiplex</td>
</tr>
<tr>
<td>3 Malformations</td>
</tr>
<tr>
<td>• Skeletal &amp; lung dysplasia</td>
</tr>
<tr>
<td>4 Neuro-developmental disorders</td>
</tr>
<tr>
<td>• Autism</td>
</tr>
<tr>
<td>• Psychomotor retardation</td>
</tr>
</tbody>
</table>

General comments
Within a context of PNSs, such diseases are only potentially hazardous to the offspring if they set in during the period of fertility. The good bearing is that many cancers are unfortunate incidents happening later in life. However, this argument is not valid to thymomas, breast cancer, various leukaemias, Hodgkin's disease, malignant monoclonal gammopathies, etc.

Clear messages of warning
• Recurrent stillbirth
• A sibling with deformities or malformations

Paraneoplastic myasthenia gravis
In thymoma-MG (occurring in about 10% of all myasthenics), the neoplasm is associated with a broad diversity of autoantibodies, some of which may cause adverse pathology to an unborn child and at the same time be of benefit to the mother.

The following onconeural antibodies are associated with thymomas:
- Anti-AChR (nicotinic adult-type)
- Anti-AChR (nicotinic foetal-type)
- Anti-AChR (nicotinic alpha3-type, ganglionic autonomic)
- Anti-vg-K channels
- Anti-Titin
- Anti-RyR1
### Anti-CV2, Anti-GAD, Anti-Hu

**Other disorders**
A variety of other autoantibodies may also be a feature, but it is beyond the scope here to elaborate more on such topics. There are indeed publications suggesting that maternal antibodies are responsible for foetal deformities or other congenital disease. It has also been suggested that some developmental disorders (e.g. autism) may be attributable to maternal antibodies; see the puzzling case history below.

**Anti-brain antibodies and autism spectrum of disorders (ASD)**
The underlying etiology for autism remains unknown, although genetic and environmental factors, including in utero environmental factors, are thought to be involved.

There is mounting evidence that maternal antibodies can target the fetal brain. Several studies have identified the presence of antibodies that bind to human fetal brain tissue in mothers with an ASD child. When anti-brain antibodies from mothers of an ASD child are administered to pregnant mice or pregnant monkeys, the offspring exhibit behavioral alterations akin to those seen in ASD children.

As reported (Brimberg et al. 2013), several studies have linked maternal infections or inflammation during pregnancy to the development of ASD in offspring, suggesting that activation of the maternal immune system might lead to an increased risk of having a child with ASD.

To further examine ties between anti-brain antibodies, autism, and autoimmunity, Dr. Diamond and colleagues screened plasma of 2431 mothers of an ASD child and 653 unselected women of childbearing age for anti-brain antibodies.

Using immunohistology on mouse brain, they found that mothers of an ASD child were nearly 4 times more likely to harbor anti-brain antibodies than unselected women of childbearing age \( P < .00001 \).

In total, 10.7% of the plasma of mothers of an ASD child (260/2431) displayed strong reactivity to mouse brain antigens compared with 2.6% of the plasma from control women (17/653). Only 28% of plasma of mothers of an ASD child showed no binding compared with 64.7% of plasma from control women.

The researchers analyzed an additional 318 plasma samples of mothers of an ASD child from a separate cohort and found that 28 (8.8%) displayed strong reactivity to mouse brain antigens. Only 22.6% (72 samples) showed no binding.

### Risk of passive transfer of PNSs
Up until now, the publications exclusively associate such foetal disorders with transplacental transfer of auto-antibodies in relation to myasthenia gravis. In view of the current data therefore, it appears that the overall risk of transferred PNSs is quite low.

**Awareness** is the key word, since preventive therapy is often possible. This may even be quite successful, see “Therapeutic considerations”. There is more specific information about how to handle the various PNSs in the sections addressing particular such disorders.

### A puzzling case history
Possibly passive transfer of ataxia and developmental disorder:
A mother of three children:
- The first one normal
- The second with autism
- The third with a severe specific language disorder

To investigate this case for passively transferable factors, maternal serum
was injected into pregnant mice. Subsequently, the mouse offspring exhibited altered motor coordination, and MRIs showed cerebellar signs. This case history started in around 1998. However, there were no findings of any cancer during a follow-up period of five years. Anyhow, it is tempting to speculate in terms of transferred autoimmunity provoked by a neoplasm, which has escaped detection.

Summary of topics related to myasthenia gravis

Embryonic-type AChR
The AChRs exist in a foetal and adult form differing only by a gamma subunit versus an epsilon one.

<table>
<thead>
<tr>
<th>Nicotinic acetylcholine receptors</th>
<th>Embryonic- and adult-types</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Diagram" /></td>
<td></td>
</tr>
</tbody>
</table>

Note the presence of either a gamma-subunit or an epsilon-subunit

Location of embryonic-type AChR
- Expressed during development
- During the last weeks of intrauterine life in humans, adult-type AChR replaces it.

Later in life, it is only expressed
- At low levels in adult human muscle
- At multiply innervated extraocular muscle fibres
- As upregulated receptor in denervated muscle
- In the myoid cells of the thymus, highlighting the hazards related to thymomas

Disorders
A. Myasthenia gravis
The finding of autoantibodies specific to foetal AChR is frequent in MG patients. For further details, please see 'Risk of passive transfer MG’ in the chapter “Paraneoplastic SPMG (thymoma)”.

B. Transient neonatal MG
This disorder is well recognized and due to transfer of maternal antibodies. Altogether, this form of MG is an observation in about 20% of infants born to myasthenic mothers.

C. Acquired arthrogryposis multiplex (AAM)
Any paralyzing agent can cause AAM, including anti-AChR antibodies that limit foetal movement, even to an extent of abolishing the AChR function. Joints cannot develop normally, unless they are regularly in motion. Foetal movements are mandatory – not just a sign of life.

Most infants with multiple congenital bent joints are diagnosed with a hereditary disorder or a disease completely unrelated to autoimmunity. Only about 2% of AAM is associated with autoantibodies.

In a myasthenia gravis context, recurrent AAM is associated with anti-AChR to the receptor of foetal type. In some of these cases, the mother did not show any evidence of MG herself, but suffered recurrent foetal loss, stillbirth or early termination. Preventive treatment during a pregnancy is an option, and the outcome may be a perfectly healthy child.
In Norway, it appears that about 2% of infants to MG mothers are born with severe skeletal anomalies, and all these children have died. To this percentage must be added all the less severe cases with only a few affected joints. The frequency of co-concurrent thymomas has not been reported in these studies. In Denmark, this paraneoplastic form of MG accounts for about 10% of all myasthenics.

**Conclusion**

*If a thymoma does not appear to co-exist in a female diagnosed with seropositive MG and planning a pregnancy, then consider a new search for this neoplasm.*
Selected references:
**Autoantibodies associated with PNS**

For a listing of myositis-specific and –overlap antibodies, please see paraneoplastic myopathies

**Table 12:** alphabetical listing of some paraneoplastic antibodies, also including some that are not strictly paraneoplastic.

<table>
<thead>
<tr>
<th>Abbreviated antibody name</th>
<th>Antibody Alias; Anti-</th>
<th>Full name of antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-AChR (adult-type)</td>
<td>nAChR (adult)</td>
<td>nicotinic acetylcholine receptor of adult-type</td>
</tr>
<tr>
<td>Anti-AChR (alpha3-type)</td>
<td>nAChR (α3)</td>
<td>nicotinic acetylcholine receptor of alpha3-type</td>
</tr>
<tr>
<td>Anti-AChR (foetal-type)</td>
<td>nAChR (foetal)</td>
<td>nicotinic acetylcholine receptor of embryonic-type</td>
</tr>
<tr>
<td>Anti-AChR (M1-type)</td>
<td>mAChR (M1)</td>
<td>muscarinic acetylcholine receptor of M1-type</td>
</tr>
<tr>
<td>Anti-AGNA</td>
<td>SOX1</td>
<td>SRY (sex determining region Y)-box 1, gial nuclear</td>
</tr>
<tr>
<td>Anti-Adenylate-Kinase 5</td>
<td>AK5</td>
<td></td>
</tr>
<tr>
<td>Anti-Alpha-enolase</td>
<td>ENO1</td>
<td>alpha-enolase 1</td>
</tr>
<tr>
<td>Anti-AMPAR</td>
<td>GluR1/R2</td>
<td>α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor</td>
</tr>
<tr>
<td>Anti-Amphiphysin</td>
<td></td>
<td>amphiphysin</td>
</tr>
<tr>
<td>ANNA3</td>
<td></td>
<td>neuronuclear antigen 3</td>
</tr>
<tr>
<td>Anti-ARHGAP26/GRAF</td>
<td></td>
<td>RhoGTPase-activating protein 26</td>
</tr>
<tr>
<td>Anti-BRSK2</td>
<td></td>
<td>BR serine/threonine kinase 2</td>
</tr>
<tr>
<td>Anti-vg-Ca-channel (P/Q-type)</td>
<td>P/Q-VGCC</td>
<td>voltage-gated calcium channel of P/Q-type</td>
</tr>
<tr>
<td>Anti-vg-Ca-channel (N-type)</td>
<td>N-VGCC</td>
<td>voltage-gated calcium channel of N-type</td>
</tr>
<tr>
<td>Anti-CARP8</td>
<td></td>
<td>carbonic anhydrase-related protein 8</td>
</tr>
<tr>
<td>Anti-CASPR2</td>
<td></td>
<td>contactin-associated protein 2</td>
</tr>
<tr>
<td>Anti-CV2</td>
<td>CRMP5, POP66</td>
<td>oligodendrocyte proteins, collapsin response mediator proteins 5, paraneoplastic oligodendrocyte cytoplasmatic protein 66</td>
</tr>
<tr>
<td>Anti-EFA6A</td>
<td></td>
<td>Exchange factor for ARF6</td>
</tr>
<tr>
<td>Anti-GAD</td>
<td>GAD67, GAD65</td>
<td>glutamic acid decarboxylase I + II or glutamic acid decarboxylase 67 and 65</td>
</tr>
<tr>
<td>Anti-Gephyrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-mGluR1</td>
<td>mGluR1</td>
<td>metabotropic glutamate receptor 1</td>
</tr>
<tr>
<td>Anti-HMGCR</td>
<td></td>
<td>3-hydroxy-3-methylglutaryl-CoA reductase</td>
</tr>
<tr>
<td>Anti-Hu</td>
<td>Hull, ANNA1, HuC, HuC, HEL-N1</td>
<td>neuronuclear antigen 1</td>
</tr>
<tr>
<td>Anti-vg-K-channel</td>
<td>VGPC, VGKC, K,1.1, K1.2, K1.6</td>
<td>voltage-gated K-channel of various subtypes</td>
</tr>
<tr>
<td>Anti-LGI1</td>
<td></td>
<td>leucine-rich, glioma inactivated 1</td>
</tr>
<tr>
<td>Anti-Ma1</td>
<td></td>
<td>membrane reactive antigen 1</td>
</tr>
<tr>
<td>Anti-Neurofilaments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-NMDAR</td>
<td></td>
<td>N-methyl-D-aspartate receptor</td>
</tr>
<tr>
<td>Anti-PCA2</td>
<td></td>
<td>Purkinje cell antigen 2</td>
</tr>
<tr>
<td>Anti-PKC gamma</td>
<td></td>
<td>protein kinase C gamma</td>
</tr>
<tr>
<td>Anti-Pyridoxal phosphatase</td>
<td></td>
<td>pyridoxal phosphatase</td>
</tr>
<tr>
<td>Anti-Recoverin</td>
<td></td>
<td>recoverin</td>
</tr>
<tr>
<td>Anti-Ri</td>
<td>Richards, ANNA2, NOVA1, NOVA2</td>
<td>neuronuclear antigen 2, neurooncological ventral antigen 1 and 2</td>
</tr>
<tr>
<td>Anti-RyR1</td>
<td></td>
<td>ryanodine receptor 1</td>
</tr>
<tr>
<td>Anti-Striated muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Anti-Ta Ma2/PNMA2</td>
<td>tumour-associated antigen membrane reactive antigen 2</td>
<td></td>
</tr>
<tr>
<td>Anti-TIFγ</td>
<td>transcriptional intermediary factor 1-gamma</td>
<td></td>
</tr>
<tr>
<td>Anti-Titin</td>
<td>titin</td>
<td></td>
</tr>
<tr>
<td>Anti-Tr PCA-Tr, Trotter, DNER</td>
<td>delta and notch-like epidermal growth factor-related receptor</td>
<td></td>
</tr>
<tr>
<td>Anti-TULIP-1 TULP1</td>
<td>tubby-like protein 1</td>
<td></td>
</tr>
<tr>
<td>Anti-UBE2E1</td>
<td>ubiquitin-conjugating enzyme E2E 1</td>
<td></td>
</tr>
</tbody>
</table>

- **Anti-Yo (xCDR2L)**
  - Young, PCA1, CDR1 (CDR34), CDR2, CDR2L (CDR62-1, CDR62-2), CDR3, PCD17-SN, CZF
  - Purkinje cell antigen 1, cerebellar degeneration related protein 34 or 62

- **Anti-ZIC4**
  - zinc finger protein 4

| ☯ = most frequent; ♪ = extracellular (plasma membrane) location |

In principle, there are at least seven categories of autoantibodies to be recognized

1. **Neuronal nuclear or nucleolar**
   - Hu (ANNA1), Ri (ANNA2), ANNA3, Ta (Ma2), Ma1, Zic4

2. **Neuronal or muscular cytoplasmatic**
   - Yo (PCA1), PCA-Tr, PCA2, Gephyrin, PKC gamma, BR-Serine / Theonine kinase 2, Adenylate-Kinase 5, CARP8, ENO1, UBE2E1, striational (Titin, RyR1, etc.)

3. **Glial**
   - CV2 (CRMP-5, POP66, oligodendrocytes), Bergman (AGNA, SOX-1), astrocytes (AQP4), ENO1

4. **Presynaptic vesicles**
   - GAD, Amphiphysin

5. **Voltage- or ligand-gated CSF or plasma membrane structures**
   - Ionotropic channels and receptors
     - AChR (adult, foetal, alpha3, M1-types), NMDAR (NR1, NR2), AMPAR (GluR1, GluR2), calcium- & potassium-channels, GlYR-alpha1
   - Metabotropic channels and receptors
     - D1, D2, GABAₐR1, mGluR1, mGluR5

6. **Other CSF membrane structures including accessory proteins**
   - AQP4, MuSK, CASPR2, gangliosides including lyso-GM1, ENO1

7. **Synaptic proteins**
   - LGI1

The group of disorders associated with antibodies to cell surface or synapptic proteins appears to be characterised by a more promising outcome of therapy – as opposed to those associated with autoantibodies to intracellular structures.
## Various currently known autoantibodies in association with CNS disorders

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Channels &amp; receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tropic</td>
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<td>Ta (Ma2)</td>
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<tr>
<td>Ma1, Zic4, Gephyrin</td>
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<td>ENO1</td>
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<tr>
<td>GAD (65, 67)</td>
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<td>AQP4, astrocytes</td>
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<tr>
<td>AGNA (SOX1), Bergmann</td>
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<td>Lyso-GM1</td>
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### Neuronal

- **Intracellular**
  - Nuclear: X X X X
  - Cytoplasmatic: X X X X X
- **Extracellular**
  - Membrane: X
  - Vesicles: X X X X X
  - Synaptic: X X X X X X
- **Glial**
  - X X X X X

### Co-occurrence of autoantibodies

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<th>Autoantibody</th>
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<th>Anti-GABA R1</th>
<th>Anti-GAD</th>
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<td>Anti-Cardiolipin</td>
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Paraneoplastic antibodies targeting the nervous system or striated muscles versus neoplasms

**Abbreviations:** AAS (acquired autonomic neuropathy, PAN); LEMS (Lambert-Eaton myasthenic syndrome); MAR (melanoma-associated retinopathy); MG (myasthenia gravis); NMJ (neuromuscular junction); PCD (paraneoplastic cerebellar degeneration); PEM (paraneoplastic encephalomyelitis); PLE (paraneoplastic limbic encephalitis); POM (paraneoplastic opsoclonus/myoclonus); PSN (paraneoplastic sensory neuronopathy, also SSN); SCLC (small-cell lung cancer); SPS (stiff-person syndrome)

**Anti-AChR**
There are different types of ligand-gated acetylcholine receptors. With a postsynaptic location at the NMJs, there are the nicotinic adult- & foetal-types (paraneoplastic MG) and presynaptic, the muscarinic AChRs of M1-type (LEMS). At ganglia, these receptors are of alpha3-type (autonomic neuropathy). There are no PNS associated with AChRs of the CNS, which also differ quite substantially from those mentioned above. The nicotinic AChRs function as regulated ion channels, whereas the muscarinic AChRs activate other ionic channels through a second messenger cascade.

The most frequent associated neoplasms are thymoma (MG, AAS) and SCLC (LEMS, AAS).

**Anti-AGNA (SOX1, glial nuclear)**
The target is nuclear structures of the Bergmann glia (anti glial nuclear antibodies = AGNA) in the Purkinje cell layer.

SOX1 (for Sex determining region Y-box 1) is a transcription factor in the Sox protein family. SOX1 expression is restricted to neuroectoderm in the tetrapod embryo. SOX1 is involved in early central nervous system development, where it is functionally redundant with SOX3 and to a lesser degree SOX2, and maintenance of neural progenitor cell identity. SOX1 is expressed particularly in the ventral striatum, and Sox1-deficient mice have altered striatum.

These antibodies are a feature of SCLC and the following PNS: LEMS, PEM (limbic encephalitis) and maybe PCD.

**Anti-Alpha-enolase (ENO1)**
This antibody is associated with paraneoplastic retinopathy and Hashimoto's encephalopathy. The target is the N-terminal region (amino terminal) of alpha-enolase. In a PNS context, this protein is located in retinal ganglion cells and inner nuclear layer cells.

The most frequent associated neoplasms are SCLC and melanoma (MAR).

**Anti-Adenylate Kinase 5 (AK5)**
A few cases with limbic encephalitis refractory to corticosteroids, IVIg and plasma exchange have been reported. Serum/CSF antibodies reacted with the cytoplasm of neurons. Probing of a hippocampal cDNA library resulted in the isolation of adenylate kinase 5 (AK5). Human AK5-affinity purified antibodies reproduced the neuronal immunolabeling of patients' antibodies.

**Anti-AMPAR (GluR1, GluR2)**
The target is the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPAR, a glutamate receptor of the ionic type.)

The clinical features are limbic encephalitis with seizures and more. The associated neoplasms are SCLC, non-SCLC, thymoma and breast cancer.
Anti-Amphiphysin
Amphiphysin is the predominant antigen in stiff-person syndrome, PEM and other PNS. It is a neuronal protein - an adapter molecule - highly concentrated in nerve terminals. This presynaptic cytoplasmatic protein (128 kDa) is located both in the CNS and at the NMJs, and it is abundant. Amphiphysin as well as dynamin and synaptojaninin all have a putative role in synaptic vesicle recycling. The two isoforms appears to act in concert as a heterodimer.

The most frequent associated neoplasms are SCLC (PEM, PLE) and breast cancer (SPS, POM).

ANNA3
The neuronuclear antigen 3 (170 kDa) is located at the nuclei of Purkinje cells, and accordingly this autoantibody is associated with paraneoplastic cerebellar degeneration.

The most frequent associated neoplasm is SCLC.

Anti-ARHGAP26/GRAF
The antigen is RhoGTPase-activating protein 26.

This onconeural antibody is associated with cerebellar ataxia and ovarian cancer.

Anti-BRSK2
The antigen is BR serine/threonine kinase 2, a protein also known as SAD1B kinase, and preferentially expressed in the brain and testis and implicated in neuronal polarization as well as synaptic development.

This onconeural antibody is associated with limbic encephalitis and ovarian cancer.

Anti-CARP8
The antigen is RhoGTPase-activating protein 8 located in the Purkinje cell cytoplasm & dendrites and at the lateral nuclei of thalamus. The typical finding is a pure paraneoplastic cerebellar syndrome (PCD).

The most frequent associated neoplasm is melanoma.

Anti-CASPR2
The target is contactin-associated protein-2, a part of some voltage-gated potassium channel complex.

Mainly, the expression of CASPR2 is at myelinated nerves confined to the axon at the juxtaparanodal region and at some isolated paranodal loops. In the juxtaparanodal region, CASPR2 precisely co-localized with Shaker-like potassium channels. CASPR2 specifically associated with Kv1.1, Kv1.2, and their Kv-beta-2 subunit. This association involves the C-terminal region of CASPR2. It has been suggested that CASPR2 may stabilize the localization of potassium channels in the juxtaparanodal region, and that CASPR2 family members may play a role in the local differentiation of the axon into distinct functional subdomains.

The typical clinical diagnoses are: acquired neuromyoyonia (Morvan’s syndrome) or limbic encephalitis.

The most frequent associated neoplasm is thymoma.

Anti-CV2 (CRMP5, CRMP2-4, POP66
There are more than 11 associated PNS with this target, which belongs to a family of ~66 kDa CNS proteins. One of the names is CRMP for collapsin response mediator proteins. The CRMP family is composed of five cytosolic phosphoproteins and highly expressed throughout the brain during development. CRMP5 is the main

Such autoantibodies are associated with the LEMS and most frequently SCLC.
antigen recognized by anti-CV2 antibodies, whereas the recognition of other members is inconsistent, such as CRMP2, CRMP3 or CRMP4. Another name for this target is paraneoplastic oligodendrocyte cytoplasmatic protein 66. It is co-associated with amphiphysin. It appears to be directly or indirectly associated with neuron survival. CV2 is a cytoplasmatic antigen of oligodendrocytes, located in the cerebellum, basal ganglia, brainstem, spinal cord & optic chiasm.

The most frequent associated neoplasms are SCLC (PEM, PLE, SSN, PCD (thymoma), POM, chorea, and optic neuritis.

**Anti-EFA6A (Pleckstrin and Sec7 domain protein)**

ADP-ribosylation factor 6 (ARF6) is a small GTPase known to regulate actin remodelling and membrane traffic. Exchange factor for ARF6 (EFA6A) is a protein that interacts with a member of the two-pore-domain potassium channel family and is involved in the regulation of the dendritic development of hippocampal neurons.

The most frequent associated neoplasm is ovarian teratoma. PEM with psychiatric symptoms, seizures and central hypoventilation are typical clinical features.

**Anti-GAD (GAD65, GAD67)**

In mammals, GAD (glutamate decarboxylase) exists in two isoforms encoded by two different genes, Gad-II (GAD65, 585 amino acids) and Gad-I (GAD67, 594 amino acids) and with molecular weights of 65 and 67 kDa, respectively. The amino acid sequence of both is with about 65 % homology (primarily in middle and C-terminal regions). The central region, which contains the decarboxylase catalytic domain, appears to be highly immunoreactive.

Exclusively, the expression of GAD65 is at GABA-ergic nerve terminals, which co-localizes with Amphiphysin and CV2 (CRMP5) while GAD67 is spread evenly throughout the cells. This difference is thought to reflect a functional difference; GAD67 synthesizes GABA for neuron activity unrelated to neurotransmission, such as synaptogenesis and protection from neural injury. This function requires widespread, ubiquitous presence of GABA. GAD65, however, synthesizes GABA for neuro-transmission, and therefore is only necessary at nerve terminals and synapses.

Anti-GAD65 is also a feature of diabetics. Upon incubation of nerve cells with serum or CSF from diabetics, there is no inhibition of the synthesis of GABA, whereas this happens with serum or CSF from PNS patients, and even in a dose-dependent manner. Accordingly, the anti-GAD appears to recognize different epitopes.

The antibodies are associated with SPS and the following neoplasms: breast, SCLC and thymoma.

**Anti-Gephyrin**

The target is a protein, which is associated with inhibitory neurotransmitter receptors. It is a bi-functional protein and essential for both synaptic clustering of inhibitory neurotransmitter receptors in the CNS and the biosynthesis of the molybdenum cofactor in peripheral tissues. It co-purifies with the inhibitory glycine receptor. Gephyrin is responsible for clustering GlyRs to postsynaptic sites by linking the GlyRβ subunit to the cytoskeleton. Moreover, in all brain areas containing synapses, there is a density of this protein.

The antibody is associated with the SPS, multiple myeloma and undifferentiated neoplasm.

**Anti-HMGCR** (alias 3-hydroxy-3-methylglutaryl-CoA reductase)

Normally in mammalian cells this enzyme is suppressed by cholesterol derived from the internalization and degradation of low density lipoprotein (LDL) via the LDL receptor. Competitive inhibitors of the reductase induce the expression of LDL receptors in the
liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol, an important determinant of atherosclerosis.

This autoantibody is associated with acute necrotizing myopathy (polymyositis?); sporadic inclusion-body myositis; polymyositis / dermatomyositis

**Anti-mGluR1**
The target is the metabotropic glutamate receptor 1 located as follows: in the cerebral cortex (superficial layer); the cerebellum (Purkinje cell bodies & spines); glomeruli of olfactory bulb (neurons & neurophilis); hippocampus; thalamus; superior colliculus; spinal trigeminal nucleus.

These antibodies are a feature of Hodgkin’s disease also exhibiting PCD.

**Anti-Hu (Hull, ANNA1)**
Hull was the pioneer to find this antibody. The target is called neuronal nuclear antigen 1 (35-40 kDa), a structure of all neurons in both the CNS and the peripheral nervous system.

These antibodies react with a group of 35- to 40-kilodalton neuronal RNA-binding proteins, including HuD, PLE21/HuC, and Hel-N1. Nuclear and cytoplasmic staining of CNS neurons demonstrates the presence of these antibodies. A ubiquitous protein, HuR, is also an antigenic target. The neuronal proteins are homologous to the embryonic lethal abnormal visual (ELAV) protein in *Drosophila* species. Anti-Hu antibodies may alter the production of these proteins, which are essential for the development, maturation, and maintenance of the vertebrate nervous system. Intrathecal synthesis of anti-Hu antibodies may represent an autoimmune cross-reaction with neurologic tissue, triggered by a remote carcinoma.

In about 70% of patients with the anti-Hu syndrome, the initial target of the disease is the dorsal root ganglia, which has a robust expression of four Hu homologues. In assays, either recombinant full length Hu-D sequence or peptide fragments are used.

Almost all cases of PEM with anti-Hu antibodies are related to small-cell lung carcinoma. The human Hu proteins are also abundant in most neuroblastomas. In fact, anti-Hu is the most frequently encountered onconeural antibody.

It is associated with the following neoplasms: SCLC, breast, ovarian, testicular, prostate, thymoma, neuroblastoma and more. Apart from stiff-person syndrome, this antibody is associated with all the other PNSs, and in particular SSN & PEM. This antibody may also be a finding in primary lateral sclerosis (PLS), and associated with adenocarcinoma in gall bladder and duodenum.

**Anti-vg-K-channel (VGKC, Kv1.1, Kv1.2, Kv1.6)**
There is an abundance of voltage-gated K-channel types. There are only three members of the Shaker-related subfamily A, and which are relevant to PNS: Kv1.1; Kv1.2; Kv1.6. These channels are inward rectifiers.

Within a PNS context, such channels have previously been reported to be targets at limbic structures, basal ganglia and at presynaptic MNJs. Such channels are also located at nodes and internodes of peripheral nerves. CASPR2 and LGI1 are accessory proteins of such potassium-channel, together forming complexes. It appears that – in a PNS context – CASPR2 is the true target. See anti-CASPR2

The associated neoplasms are SCLC and thymoma.

**Anti-LGI1 (Leucine-rich, glioma inactivated 1)**
It is a secreted synaptic protein, which associates with VGKCs and AMPA receptors via the ADAM proteins.

LGI1 is a ligand for ADAM22 that positively regulates synaptic
transmission mediated by AMPA-type glutamate receptors. The molecular function of ADAM22 is as a receptor, and it is highly expressed in the brain. ADAM23 can bind to LGI1, and is also highly expressed in the brain, prominently in the amygdala, caudate nucleus, hypothalamus, thalamus, cerebral cortex and occipital pole. LGI1 regulates voltage-gated potassium channels assembled from KCNA1, KCNA4 and KCNAB1. LGI1 slows down channel inactivation by precluding channel closure mediated by the KCNAB1 subunit.

Moreover, this protein appears to play a role in the control of neuroblastoma cell survival: expression is reduced in low-grade brain tumours and significantly reduced or absent in malignant gliomas.

It is associated with the following neoplasms: thyroid, lung, thymoma, ovarian teratoma and more. The paraneoplastic disorder is limbic encephalitis with seizures and hyponnaatriaemia.

**Anti-Ma1**

The name of this protein is membrane reactive antigen 1. It is a combined 37 and 40 kDa neuronal (subnucleus) & testicular germ cell protein with homology to Ma2 (see anti-Ta below).

The main features of anti-Ma syndromes are brainstem dysfunction with EOM limitation, dysphagia, cerebellar disorders with ataxia of trunk and extremities. In addition, sensory loss and myokymia may be other characteristics. The associated tumours are as follows: breast, lung (large-cell) and colon.

**Anti-NMDAR**

The targets are neurofilament proteins of the perikaryal type, which undergo transformation and transport into the axonal type. Clinically, POM is the characteristic feature.

The most common associated neoplasms are SCLC and neuroblastoma.

**Anti-NMDAR (NR1)**

The target is the N-methyl-D-aspartate receptor (NMDAR, a glutamate receptor of the ionic type.) The NMDA receptor is distinct in that it is both ligand-gated and voltage-dependent. Activation of NMDA receptors results in opening of an ion channel that is non-selective to cations. This allows flow of Na+ and small amounts of Ca2+ ions into the cell and K+ out of the cell. Presumably, calcium flux through NMDARs plays a critical role in synaptic plasticity, a cellular mechanism for learning and memory. N-methyl-D-aspartate is the name of its specific agonist.

The associated neoplasm is a teratoma, the most common tumour in new-borns. Mature cystic teratomas account for 10-20% of all ovarian neoplasms. Not only are they the most common ovarian germ cell tumour but also the most common ovarian neoplasm in patients younger than 20 years. The incidence of all testicular tumours in men is 2.1-2.5 per 100,000. Germ cell tumours represent 95% of testicular tumours after puberty, but pure benign teratomas of the testis are rare, accounting for only 3-5% of germ cell tumours. The incidence of all testicular tumours in prepubertal boys is 0.5-2 per 100,000, with mature teratomas accounting for 14-27% of these tumours. Benign teratomas of the mediastinum are rare, representing 8% of all tumours of this region.

Anti-NMDAR is associated with a particular type of limbic encephalitis characterised by neuropsychiatric features, troubled memory, seizures,
dyskinesias, dystonia, decreases consciousness, sleep disorder and more (dyskinetic encephalitis lethargica).

**Anti-PCA2**
The antigen is a 280 kDa neuron-specific protein, located in the cytoplasm of Purkinje cell in soma & dendrites. Typically, the associated neoplasm is SCLC, also explaining that these autoantibodies may co-exist with anti-vg-Ca-channel (P/Q- & N-type) and anti-AChR (of muscle & neuronal type).

Clinically, anti-PCA2 is associated with PCD. Attributable to the co-existing onconeural antibodies listed above, PLE, LEMS, AAS and a motor syndrome may also be present.

**Anti-Protein kinase C gamma (anti-PKC gamma)**
Paraneoplastic cerebellar degeneration also occurs in patients with non-SCLC and without typical onconeural antibodies - and is associated with immune reactions against key proteins of the Purkinje cells – such as PCK gamma.

**Anti-Pyridoxal phosphatase**
Pyridoxal phosphatase is a co-enzyme of vitamin B6 (pyridoxine). The antigen is located at both the central and the peripheral nervous system. Deficiency of vitamin B6 is usually associated with seizures and sensory-motor neuropathy. A seropositive finding may be a feature of about 9% of patients with lung cancer and of 7% with other neoplasms, for example well-differentiated thyroid cancer and of autoimmune thyroid disease.

PNS associated with this antibody are awaiting discovery.

**Anti-Ri (Richards, ANNA2, NOVA1, NOVA2)**
Richards was the first to report the finding of these antibodies. The names of the targets are also neuronuclear antigen 2 and neuro-oncological ventral antigen 1. The CNS antigens are either a 55-kDa protein (Nova; RNA binding) or an 80-kDa protein. There are no such targets in the peripheral nervous system. The characteristic clinical features are PCD or a movement disorder with myoclonus / opsoclonus, triggered by visual fixation.

Frequently, other onconeural antibodies are co-existing. Therefore, a variety of other PNS is associated: encephalopathy, myelopathy, peripheral neuropathy (sensory-motor; polyradiculopathy; cranial neuropathy: VI; VIII [deafness or tinnitus]), laryngospasm, dystonia (jaw opening or neck), LEMS, visual blurring, incontinence.

The typical associated neoplasms are located at breast or lung (both SCLC & non-SCLC).

**Anti-Recoverin**
The target is a 23-kDa photoreceptor protein in the retina. The associated neoplasms are SCLC and melanoma. CAR is the clinical feature.

**Anti-RyR1**
The target is the ryanodine receptor 1 of striated muscles. The main immunogenic regions are epitopes at the C-terminus (AA 5019-5038) and at the C-terminus transmembrane (AA 4997-5017) regions. These receptors function as calcium release channels.

The autoantibodies are associated with paraneoplastic MG (thymoma). Moreover, they are a feature of non-paraneoplastic late-onset MG.

**Anti-Striated muscle (unspecific)**
Immunohistochemistry is the method to detect such antibodies. Accordingly, unspecific binding of IgG to various epitopes of striated muscles is the finding.

These autoantibodies are associated with thymoma, paraneoplastic myasthenia gravis, and rippling muscle syndrome. See also anti-Titin and anti-RyR1.

**Anti-Ta (Ma2, PNMA2)**
The target is tumour-associated antigen or membrane-reactive antigen 2. It is a 41.5-kDa protein located in the subnucleus of neurons. There is homology to Ma1.

In about 90%, the patients present with isolated or combined limbic, diencephalic or brainstem dysfunction (PEM). Excessive daytime sleepiness may also be an observation, and in such cases decreased / absent hypocretin-1 may be a feature of the CSF. In young male patients, the primary tumour is in the testis. In other patients, the most frequent neoplasms are lung adenocarcinoma, colon or breast cancer.

**Anti-TIFγ (transcriptional intermediary factor 1-gamma)**

This factor plays a role in the control of cell proliferation.

The autoantibody is associated with polymyositis / dermatomyositis, and in particular cancer associated dermatomyositis (CADM) with 58 % of co-existing neoplasms in anti-Tifγ seropositive cases.

**Anti-Titin**

The target is the giant protein titin of striated muscles. This is the largest molecule of the body, functioning as a giant spring.

The autoantibodies are associated with paraneoplastic MG (thymoma), although they are also a frequent finding in non-paraneoplastic late-onset MG. The titres appear to correlate with the severity of MG, possibly attributable to a co-existing myopathy. Such autoantibodies are a feature of healthy controls in only about 0.4%, so they are of a high diagnostic value.

In myasthenic patients, the detection of these autoantibodies should be by a method using the main immunogenic region (MIR, for example MGT-30-peptide). In sporadic rippling muscle syndrome, the antibodies are to the titin isoform N2A.

**Anti-Tr (Trotter, PCA-Tr)**

Trotter discovered this antibody. The antigen is located at the cytosol and outer surface of the endoplasmic reticulum, and typically found in Purkinje cell cytoplasm and dendrites.

The antigen is the delta and notch-like epidermal growth factor-related receptor (DNER).

The associated cancer is Hodgkin’s lymphoma. Interestingly, the neoplasm is only rarely stained by the antibody.

PCD is the typical neurological feature. Variant syndromes may be a reversible limbic encephalitis and optic neuritis.

**Anti-TULIP-1 (TULP1)**

Tubby-like protein 1 is a photoreceptor-specific protein. It co-localises and interacts with actin in photoreceptor cells of the retina. In humans, there are two genes, TULP1 and TULP2. The expression of TULP1 is exclusively in retina, whereas TULP2 is located in both retina and testis.

Paraneoplastic retinitis is the clinical finding.

**Anti-Ubiquitin-conjugating enzyme E2E1 (UBE2E1)**

The modification of proteins with ubiquitin is an important cellular mechanism for targeting abnormal or short-lived proteins for degradation. Ubiquitination involves at least three classes of enzymes: ubiquitin-activating enzymes, or E1s, ubiquitin-conjugating enzymes, or E2s, and ubiquitin-protein ligases, or E3s. This gene encodes a member of the E2 ubiquitin-conjugating enzyme family. Three alternatively spliced transcript variants encoding distinct isoforms have been found for this gene.

Paraneoplastic encephalomyelitis and SCLC are associated.

**Anti-Yo (Young, CDR1 (CDR34), CDR2, CDR2L (CDR62-1, CDR62-2), CDR3, PCD17-SN, CZF)**
Young was the first to report the finding of these antibodies. The names of the targets are also Purkinje cell antigen 1 and cerebellar degeneration related proteins 34 & 62. They are proteins of the Purkinje cell cytoplasm (ribosomes – both membrane bound & free – and Golgi apparatus) and various neoplasms: 34kDa (CDR34); 62kDa (CDR62-1, CDR62-2, leucine zipper); CDR3 (leucine zipper); 52kDa (PCD17-SN, leucine zipper); 58kDa (CZF, zinc finger); CDR2L is localized to the cell membrane.

The following PNS are associated: PCD, PLE and SPS. The most frequent neoplasm is breast cancer (95%). Other cancers may be SCLC, ovarian, prostatic, oesophagus, gastric, parotid.

**Anti-ZIC4**

The zinc finger (Zic) proteins have important roles in the development of the nervous system, and comprise a family of five zinc-finger proteins with extensive sequence homology (range 52%-62% identity). Because the Zic proteins are highly homologous to each other, the sera of patients with anti-Zic4 antibodies usually react with Zic1, and less frequently with Zic2. The anti-Zic4 antibodies show predominant reactivity with the nuclei of neurons of the granular layer of the cerebellum and less intense reactivity with other neurons, including in descending order Purkinje cells, and neurons of deep cerebellar nuclei, brainstem and brain.

**SCLC** is the associated neoplasm, and PCD is the typical neurologic finding. A combined finding of anti-ZIC4 and other onconeural antibodies is typical in PEM. Detection of Zic4 antibodies often associates with anti-Hu or CV2 (CRMP5) antibodies. Patients with isolated Zic4 antibodies are more likely to develop cerebellar dysfunction than those with concurrent other autoimmunities.

**Table 13:** The most frequently encountered onconeural autoantibodies and their associated neoplasms, and accounting for about 60% of all PNS cases

<table>
<thead>
<tr>
<th>Onconeural antibody</th>
<th>Neoplasms</th>
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<tr>
<td><strong>by decreasing order of occurrence</strong></td>
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<tr>
<td>Anti-Hu</td>
<td>SCLC, breast, ovary, testis</td>
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<tr>
<td>Anti-Yo</td>
<td>Breast, ovary, SCLC</td>
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<td>Anti-CV2 (CRMP5)</td>
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<tr>
<td>Anti-Ta (Ma2, PNMA2)</td>
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<td>Anti-Amphiphysin</td>
<td>Breast (98%), SCLC</td>
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<tr>
<td>Anti-Ri</td>
<td>SCLC, breast, ovary</td>
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### Neoplasms versus Antibodies

**Primary analyses**

- Breast
- Colon (rectum)
- Hodgkin's disease
- Lung (adenocarcinoma)
- Lung (small cell, SCLC)
- Mediastinum, undiff.
- Melanoma
- Multiple myelomas
- Neuroblastoma
- Oesophagus
- Ovary
- Pancreas
- Parotid
- Prostate
- Stomach
- Testis
- Thymus
- Uterus (sarcoma)
Recommended diagnostic criteria for paraneoplastic neurological syndromes.


J Neurol Neurosurg Psychiatry 2004; 75 (8): 1135-1140.
Comment in: J Neurol Neurosurg Psychiatry 2004; 75 (8): 1090.

BACKGROUND: Paraneoplastic neurological syndromes (PNS) are defined by the presence of cancer and exclusion of other known causes of the neurological symptoms, but this criterion does not separate "true" PNS from neurological syndromes that are coincidental with a cancer. OBJECTIVE: To provide more rigorous diagnostic criteria for PNS. METHODS: An international panel of neurologists interested in PNS identified those defined as "classical" in previous studies. The panel reviewed the existing diagnostic criteria and recommended new criteria for those in whom no clinical consensus was reached in the past. The panel reviewed all reported onconeural antibodies and established the conditions to identify those that would be labelled as "well characterised". The antibody information was obtained from published work and from unpublished data from the different laboratories involved in the study.

RESULTS: The panel suggest two levels of evidence to define a neurological syndrome as paraneoplastic: "definite" and "possible". Each level can be reached combining a set of criteria based on the presence or absence of cancer and the definitions of "classical" syndrome and "well characterised" onconeural antibody.

CONCLUSIONS: The proposed criteria should help clinicians in the classification of their patients and the prospective and retrospective analysis of PNS cases.

In short
Ideally, no other possible explanation than remote effect of cancer should be an option.
- Symptoms & signs consistent with PNS.
- Inclusion & exclusion criteria see "Definition of PNS" elsewhere in this book.
- An investigation resulting in specific findings consistent with what is referenced in the various PNS chapters of this book.


Download the whole report from here: CV2

Paraneoplastic Neurological Syndrome Euronetwork.
PNSEURONET: http://www.pnseuronet.org/

Summary

An overview of the management of classical PNS, i.e. paraneoplastic limbic encephalitis, subacute sensory neuronopathy, paraneoplastic cerebellar degeneration, paraneoplastic opsoclonus-myoclonus, Lambert-Eaton myasthenic syndrome and paraneoplastic peripheral nerve hyperexcitability is given. Myasthenia gravis and paraproteinemic neuropathies are not included in this report. No evidence-based recommendations were possible, but good practice points were agreed by consensus. To allow tumour therapy to be started early and further to prevent progressive neuronal death and irreversible disability, urgent investigation is indicated. This is particularly true in central nervous system (CNS) PNS syndromes.

Onconeural antibodies are of great importance in the investigation of PNS and can be used to focus tumour search. PDG-PET is useful if the initial radiological tumour screen is negative. Early detection and treatment of the tumour is the approach that seems to offer the greatest chance for PNS stabilization. Immune therapy usually has no or modest effect on many of the CNS syndromes, whereas such therapy is beneficial for PNS affecting the neuromuscular junction. Symptomatic therapy should be offered to all patients with PNS.
Listing of some books and reviews


Dalmay, J, Rosenfeld M. Chapter 51 – Paraneoplastic Neurologic Syndromes


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Short compendium
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Channelopathies, receptor and solute carriers disorders in neurology, please see separate compendium

Channelopathies
receptor and solute carrier
disorders in neurology

Autoantibodies and biomarkers of neurological disorders

Version 3.1, February 2014

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