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What a Clinician Must Know Regarding Diagnosis of Paraneoplastic Neurological Syndromes

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Abstract: Paraneoplastic neurological syndromes (PNS) are rare, immune-mediated effects of a systemic cancer. PNS may affect the central and/or peripheral nervous system. Most often, the neurological symptoms precede the cancer diagnosis. The clinician must be aware of the various PNS, as early acknowledgement of such syndromes facilitates early cancer diagnosis and might improve the prognosis. Onconeural antibodies are important diagnostic markers for PNS and approximately 50 % of the patients with PNS have antibodies. The PNS diagnosis is confirmed if such antibodies are present in the serum and/or spinal fluid. Supplementary investigations include MRI, EEG, and spinal fluid analysis, and these are often of diagnostic help for the diagnosis of limbic encephalitis or other paraneoplastic manifestations of the central nervous system. Neurophysiological tests are usually required to verify paraneoplastic neuropathy or neuronopathy. CT scans are used for cancer screening, but total body PDG-PET scan may be more sensitive in detecting small tumours. PDG-PET can also exhibit pathologic features in cases of limbic encephalitis, where MRI has not shown hypersignal. Other targeted investigations, such as ultrasound and various serological markers for cancer, may also be required to detect an underlying malignancy. **EANO Mag 2012; 2 (2): 67–70.**

Key words: paraneoplastic neurological syndrome, onconeural antibody, detection

Onconeural Antibodies and Other Neuronal Antibodies

About 3–5 % of patients with small-cell lung cancer and 15–20 % of patients with thymoma develop paraneoplastic neurological syndromes (PNS). Less than 1 % of patients with other types of tumours develop paraneoplastic neurological symptoms [1]. As PNS are also associated with some benign tumours, eg, teratoma and thymoma, malignant properties are not a necessary component of the tumour, but expression of a relevant protein is necessary for the development of a PNS.

Tumours in patients with PNS express proteins that are normally only expressed in the nervous system. The tumour protein is identical to the neuronal protein, but is identified as foreign or non-self by the immune system when expressed by the tumour cell. The body produces antibodies and activates T-cells to these proteins as part of the anti-tumour immune response. The antibodies and T-cells cross the blood-brain or blood-nerve barriers and cross-react with proteins in the nervous system. This cross-reaction leads to loss of neuronal cells and development of neurological symptoms [2, 3].

The well-characterized onconeural antibodies are anti-Hu, anti-Yo, anti-CRMP5, anti-amphiphysin, anti-Ma, anti-Ri, and anti-Tr [4, 5]. The presence of one of these antibodies in a patient with neurological symptoms defines the diagnosis as definite PNS whether a tumour is detected or not [4]. There is a strong association between onconeural antibodies and cancer; > 95 % of patients with a well-characterized antibody will be diagnosed with cancer and detection of antibodies should therefore lead to a thorough screening for an underlying tumour [6]. As the detection of paraneoplastic antibodies precedes the cancer in most of the cases, routine follow-up of patients with onconeural antibodies where no cancer is detected should be performed for at least 4 years [7]. The majority of tumours are, however, detected within the first 2 years after onset of neurological symptoms. Table 1 lists an overview of the well-characterized onconeural antibodies, PNS, and their associated cancers.

The association between onconeural antibodies, cancer, and PNS is complex, as there are few antibodies specific for one type of PNS or cancer. However, in a clinical context, we often deal with a set of neurological symptoms suspected to be a PNS together with an onconeural antibody. We know that the well-characterized onconeural antibodies predict the location of the tumour more accurately than the type of PNS, and this facilitates the further investigation with regard to an underlying malignancy [8].

Approximately 50 % of the patients with PNS are seropositive for onconeural antibodies. In other words, half of the patients with PNS have no detectable antibodies and this emphasizes the point that absence of antibodies does not exclude the PNS diagnosis.

Onconeural antibodies are important diagnostic tool. The clinical manifestations of PNS often appear early in the cancer development, while the tumour is still small [9, 10], and

Table 1. Well-characterized onconeural antibodies, paraneoplastic neurological syndromes (PNS), and predominantly associated tumours.

Antibody	PNS	Tumour
Hu	PEM	SCLC, other
Yo	PCD	Ovary, breast
Ri	PEM, POM	Breast, SCLC
Amphiphysin	PEM, stiff person syndrome	Breast, SCLC
CRMP5	PEM, PCD, chorea, neuropathy	SCLC, thymoma
Ma	PEM	Testicular, SCLC
Tr	PCD	Hodgkin lymphoma

PEM: paraneoplastic encephalomyelitis; PCD: paraneoplastic cerebellar degeneration; POM: paraneoplastic opsoclonus-myoclonus; SCLC: small-cell lung cancer

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the type of antibody can give indications as to where the cancer originated [2, 8]. The cancer can then be identified at an earlier stage, specific tumour treatment can be initiated, and the chance for better neurological recovery is increased. Anti-Hu and anti-Yo are the most common antibodies in PNS in general [5, 10]. Anti-Hu is often associated with small-cell lung cancer, while anti-Yo is normally associated with ovarian and breast cancers [5, 11].

Partly characterized onconeural antibodies include anti-GluR, which are associated with paraneoplastic cerebellar degeneration and Hodgkin's lymphoma, anti-Zic4, which are associated with paraneoplastic cerebellar degeneration and small-cell lung cancer, and anti-SOX, which are associated with Lambert-Eaton myasthenic syndrome and small-cell lung cancer [1, 12].

A number of other neuronal antibodies are sometimes associated with paraneoplastic syndromes and tumours, but less strictly and they may be present in patients with neurological syndromes, without a tumour. These include anti-NMDAR (encephalitis and teratoma), anti-AMPAR (encephalitis and various cancers), anti-VGKC complex, including anti-Lgi1 and Caspr2 (encephalitis, Morvan syndrome, neuromyotonia, and small-cell lung cancer), anti-AChR (myasthenia gravis and thymoma), anti-ganglionic AChR (pandysautonomia and small-cell lung cancer), anti-GAD (stiff person syndrome, cerebellar ataxia, encephalitis, and thymoma), and anti-VGCC (Lambert-Eaton myasthenic syndrome and small-cell lung cancer [1, 12].

In the following, only PNS associated with the well-characterized onconeural antibodies will be briefly reviewed.

Paraneoplastic Neurological Syndromes

PNS is a heterogeneous group of syndromes. To ensure a common diagnostic understanding, Graus et al [4] set up a list of criteria to define PNS in 2004. This consensus report divided PNS into definite and possible PNS based on the detection of well-characterized onconeural antibodies, neurological symptoms, and presence or absence of cancer. Syndromes that are most often associated with cancer and onconeural antibodies are defined as classical PNS. Among these are paraneoplastic encephalomyelitis, paraneoplastic limbic encephalitis, paraneoplastic cerebellar degeneration, paraneoplastic sensory neuronopathy, and paraneoplastic opsoclonus-myoclonus. Lambert-Eaton myasthenic syndrome and dermatomyositis are also classical PNS, but they are less often associated with cancer. Non-classical PNS are diseases in which the patients show diverse neurological symptoms, but well-characterized onconeural antibodies are not detected. Giometto et al reported that 18 % of all patients with definite PNS had no onconeural antibodies [13].

PNS may affect all parts of the central or peripheral nervous system. Anti-Yo-mediated paraneoplastic cerebellar degeneration is characterized by loss of Purkinje cells, leading to ataxia [14]. The classical symptoms of limbic encephalitis are neuropsychiatric features, including anxiety, depression and dementia, loss of short-term memory, and seizures, which are due to medial temporal lobe affection. Paraneoplastic limbic encephalitis is associated with anti-Hu, anti-Ma, anti-CRMP5, anti-amphiphysin, and anti-Ri [1–3, 5, 15]. Paraneoplastic encephalomyelitis potentially affects most of the central nervous system, including the limbic system, cerebellum, basal ganglia, brainstem, and spinal cord, and is associated with anti-Hu, anti-CRMP5, anti-Ri, anti-Ma, and anti-amphiphysin [1–3, 5, 15]. Sensory and autonomic nerves can also be affected, either as an isolated paraneoplastic peripheral neuropathy or as part of paraneoplastic encephalomyelitis. Paraneoplastic sensory neuronopathy can affect limb, trunk, and cranial nerves, the patients complain of pain, numbness, and sensory deficits. This disorder is most often associated with anti-Hu or anti-CRMP5. Paraneoplastic opsoclonus-myoclonus affects eye movement, often in conjunction with myoclonus and truncal ataxia, and is most often associated with anti-Ri, anti-Hu, anti-amphiphysin, or anti-Ma2 [1–3, 15].

Pathogenic Mechanisms of PNS

The direct pathogenic role of onconeural antibodies has been difficult to prove. The removal of antibodies (eg, by plasmapheresis) does not cause clinical improvement in most patients with PNS. One has not succeeded to create an animal model for the classical PNS, eg, transferral of onconeural antibodies did not induce PNS in laboratory animals [12]. Several studies now indicate that PNS are T-cell-mediated and that the onconeural antibodies do not play a direct pathogenic role. However, recent laboratory research suggests that at least some of the onconeural antibodies may also induce disease. Purified IgG from patients with amphiphysin antibodies and stiff person syndrome has been injected into the subarachnoid space of rats. The rats subsequently developed symptoms similar to those seen for stiff person syndrome [16]. Furthermore, Greenlee et al have shown that rat Purkinje cells incorporate IgG, and that Yo antibodies accumulate in the cells and trigger Purkinje cell death in a non-apoptotic manner [17].

Infiltrates of mononuclear cells, neuronal degeneration, microglia proliferation, and gliosis are found at autopsy, for instance in paraneoplastic cerebellar degeneration [14]. Other autopsy findings are that patients with antibodies against intracellular antigens often show CD4+ and CD8+ T-cell infiltrates in the brain parenchyma [15]. Activated CD4+ T-cells have been found in the spinal fluid of patients with paraneoplastic cerebellar degeneration [18], while cytotoxic T-cells that recognize CDR2 have been found in the blood of anti-Yo-positive patients with paraneoplastic cerebellar degeneration [19, 20]. However, the functions of the cytotoxic T-cells in PNS remain uncertain. Ma1-activated CD4+ cells have been shown to induce encephalomyelitis in mice [21]. Tani et al found that patients with small-cell lung cancer with LEMS and Hu or Yo antibodies had lower levels of a specific subtype of regulatory T-cells, the T_{reg}Foxp3+ cells, than patients with small-cell lung cancer without PNS, and concluded that low levels of T_{reg} cells may be caused by an immune regulatory dysfunction in PNS [22]. It has also been demonstrated that epithelial ovarian cancer patients with a high CD8+/T_{reg} ratio have an improved prognosis [23].

Some patients with cancer have onconeural antibodies, but do not develop neurological symptoms [5]. Why some patients develop PNS, while others do not, remains uncertain, but the HLA haplotype has been suggested to be important. The frequency of the HLA-DQ2+ haplotype is higher in PNS patients with anti-Hu [24], while the frequency of HLA-A2.1, HLA-A24, or HLA-B27 haplotypes is higher in patients with anti-Yo [25, 26].

Some studies suggest that tumour expression of onconeural antigens invoke the body's tumour immunity response, but it has not been shown that this immunity response is beneficial. In a group of patients with SCLC and Hu-/VGCC antibodies, there was no association between the presence of antibodies and the prognosis of SCLC [27]. However, patients with onconeural antibodies often have smaller tumours, and spontaneous tumour regression has been noted in anecdotal cases [28, 29].

The pathogenic mechanisms in PNS lead to loss of neurons. In many cases, the neuronal damage has been so devastating that the patients have severely reduced life quality or die as a consequence of the paraneoplastic disease itself.

Clinical Work-Up

PNS Diagnosis

PNS is a differential diagnosis in most subacute and progressive neurological disorders. PNS should be suspected in all patients with rapidly progressive syndromes with inflammatory features, especially if both the central and peripheral nervous systems are affected. The diagnostic measures in suspected PNS should aim to exclude other aetiologies, to confirm that neurological symptoms are consistent with PNS, and to detect the underlying tumour.

Serological work-up, including measurement of onconeural antibodies, is important. For diagnostic purposes, serum testing of such antibodies is usually sufficient. However, onconeural antibodies can be detected at high levels in the spinal fluid in most patients with paraneoplastic CNS syndromes, indicating intrathecal antibody synthesis [30]. The spinal fluid usually shows signs of inflammation in the CSF, such as pleocytosis, increased protein concentration, a high IgG index, and oligoclonal bands in the spinal fluid [30, 31]. MRI of the central nervous system must be performed, but can be normal at onset. MRI usually shows hypersignal in the medial temporal lobes in paraneoplastic limbic encephalitis, which is often best visualized on coronal FLAIR sections. Initial MRI is obligatory in order to exclude differential diagnoses, such as metastases of the brain. EEG is usually performed in patients with encephalitis and may show generalized or localized encephalopathy or epileptic potentials. Paraneoplastic peripheral neuropathies are often asymmetrical and can be purely sensory, as part of a sensory neuronopathy, or a more classical axonal sensory-motor distal polyneuropathy. In these cases, nerve conduction and electromyography studies are important. Autonomic symptoms, in particular gastrointestinal dysmotility syndromes, are frequent in PNS associated with anti-Hu and anti-CRMP5 antibodies. Autonomic testing can be of use in such patients. However, the only paraclinical finding that is specific for PNS is the detection of onconeural antibodies. Not a single routine investigation exhibits features specific for PNS and in a given case of PNS all tests may even be normal.

Tumour Screening

If the primary cancer is unknown, cancer markers can be measured in the serum, such as NSE for lung cancer, CA-125 for ovarian cancer, AFP for immature teratomas and β-HCG/AFP for testicular cancer [32]. If the patient smokes, the most probable underlying cancer is SCLC. Usually, a body CT scan (neck, chest, abdomen, and pelvis) is required for a malignancy screening. Ultrasound may be used to detect testicular cancer and mammography for the detection of breast cancer. A total-body PDG-PET scan is more sensitive in the detection of small tumours, particularly in the case of mediastinal lymphadenopathy. The combined modalities of whole-body CT and FDG-PET is probably the most optimal investigation. FDG-PET can also reveal hypersignal in the temporal lobes due to limbic encephalitis, where early MRI has been normal. However, FDG-PET is not an optimal modality for autoimmune encephalitis due to the high background of glucose metabolism in the brain.

If there is strong suspicion of an underlying malignancy, a new diagnostic work-up is usually needed after approximately 6 months, and may be repeated for up to 4 years [7]. In particular, all patients with neurological symptoms and onconeural antibodies should be followed closely if a cancer is not detected initially.

There are several differential diagnoses to PNS. For encephalitis, there may be several other aetiologies: herpes virus encephalitis, Hashimoto's encephalitis, toxic-metabolic encephalopathy, Wernicke-Korsakoff's syndrome, systemic lupus erythematosus, and other kinds of angiitis of the CNS. For cerebellar ataxias, there are also several other possibilities: toxic-metabolic cerebellar degeneration, infectious or post-infectious cerebellitis, Miller-Fisher syndrome, GAD or gliadin antibody associated cerebellar ataxia, and Creutzfeldt-Jacob disease. Patients with cancer may develop PNS-like syndromes that are due to metastases, gliomatosis, or caused by chemotherapy toxicity.

In conclusion, rapid progression of neurological symptoms where no other aetiology is found, typical constellations of neurological signs, inflammatory features in the spinal fluid, and multifocal affection of the nervous system are clinical "red flags" for PNS. The detection of onconeural antibodies should lead to a thorough screening for an underlying tumour and if the first diagnostic work-up is normal, it should be repeated in the following years.

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Conflict of Interest

The authors have no conflict of interest.

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