

# PARANEOPLASTIC NEUROLOGICAL SYNDROMES DIAGNOSIS AND TREATMENT

<sup>1</sup>CORINA ROMAN-FILIP, <sup>2</sup>CIPRIAN ROCIU

<sup>1</sup>„Lucian Blaga” University of Sibiu, <sup>2</sup>County Clinical Hospital of Cluj-Napoca

**Abstract:** Paraneoplastic neurological syndromes may present classical neurological symptoms or less frequently, symptoms that do not initially raise suspicion of these disorders. Recent examples include patients with epilepsy partialis continua or frontal disequilibrium associated with Hu antibodies, hypersomnia and anti-Ma2 antibodies, Devic's syndrome and CV2/CRMP5 antibodies and a syndrome characterized by psychiatric features and central hypoventilation in young women with anti-N-methyl-D-aspartate receptor antibodies. The cause of the neuronal damage is still open to debate. The recent description of antibodies against membrane proteins in opsoclonus or encephalitis associated with teratoma strongly suggests that antibodies may be responsible for the clinical features in some cases. Early diagnosis and effective treatment of the tumor remain the best options to improve or stabilize the syndrome. Immunotherapy, including rituximab, seems effective in those cases associated with functional damage. Detection of onconeural antibodies is crucial to make the correct diagnosis. Immunotherapy should be used, although the impact of the treatment is unclear in cases with irreversible neuronal damage.

**Keywords:** paraneoplastic, limbic encephalitis, cerebellar degeneration, Eaton-Lambert syndrome, immunotherapy, antibodies

**Rezumat:** Sindroamele neurologice paraneoplazice pot prezenta la debut, simptome neurologice clasice, sau mai puțin frecvent, simptome atipice, care inițial nu ridică suspiciunea unui astfel de sindrom. Exemple recente includ pacienți care au prezentat epilepsie parțială continuă sau dezechilibru frontal asociat cu anticorpi Hu, hipersomnie și anticorpi anti Ma2 etc. Cauzele distrugerilor neuronale sunt încă neclare. Datele recente indică anticorpi anti proteină membranară în opsoclonus sau, asocierea encefalitei limbice cu teratomul ovarian sugerând că prezența anumitor anticorpi este responsabilă de simptomele neurologice. Detectarea anticorpilor onconeurali este esențială în stabilirea diagnosticului. Tratatamentul precoce și adecvat al tumorii rămâne cea mai bună opțiune pentru stabilizarea sindromului paraneoplazic. Imunoterapia pare eficientă în acele cazuri cu disfuncții neuronale funcționale, rămâne neclar aportul ei în cazurile cu leziuni neuronale ireversibile.

**Cuvinte cheie:** paraneoplazic, encefalită limbică, degenerescența cerebelară, sindrom Eaton-Lambert, imunoterapie, anticorpi

Paraneoplastic neurological syndromes (PNS) occur exclusively in the patients with different forms of cancer (table 1). PNS are rare but important in the clinical practice, due to the fact that they precede the cancer diagnosis that is usually limited in evolution, offering the best chance for a treatment. (2) Certain PNS are associated in serum and in the cerebrospinal fluid (CSF) with the presence of the antibodies against the onconeural antigens, expressed by the primitive tumour (onconeural antibodies). Most of the patients with PNS have onconeural antibodies in CSF, supporting the hypothesis that the immune response against the onconeural antigens is important in PNS pathogenesis. (16)

## Paraneoplastic encephalomyelitis

Paraneoplastic encephalomyelitis (PEM) is characterized by pathologic changes of neuronal loss, microglial proliferation, and inflammatory infiltrates in the nervous system. PEM may be associated with the classic neurological syndromes, such as the limbic encephalitis, or less frequently with symptoms that do not initially raise suspicion of PNS. In these conditions, the detection of the onconeural antibodies is crucial to make the correct diagnosis. Recent examples include patients who present epilepsy partialis continua or frontal disequilibrium associated with Hu antibodies, hypersomnia. (9, 6)

Less than 5% of the PEM patients with antiHu antibodies do not develop cancers after long term surveillance. A recent study confirmed the fact that there were no differences between the PEM cancer patients with positive HU and those PEM Hu without cancer and that all the patients with Hu antibodies required regular examinations in order to detect malignities, irrespective of age and the habit of smoking. (6)

## Limbic encephalitis

The classic syndrome of the limbic encephalitis includes the rapid development of a clinical picture with predominating psychical manifestations, irritability, depression, sleeping disorders, epileptic crises,

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hallucinations, affection of short term memory. Recent studies (8) talk about a useful clinical classification of the immune mediated encephalitis in four groups,

corresponding to the type and location of antigens (table 2).

**Table no. 1. Paraneoplastic neurological syndromes**

<b>Syndromes of the central nervous system</b>	Encephalomyelitis Limbic encephalitis Cerebral trunk encephalitis Subacute cereberall degeneration Opsoclonus-myoclonus (b) Optic neuritis (b) Stiffman syndrome Necrotic myelopathy (a) Diseases of the motor neuron (a)
<b>Syndromes of the peripheral nervous system</b>	Subacute sensitive neuropathy Subacute/chronic sensitive and motor neuropathies (b) Vasculitis neuropahty (a) Chronic gastrointestinal pseudoobstruction
<b>Muscular and neuromuscular junction syndrome</b>	Myasthenia gravis (a) Lambert-Eaton myasthenic syndrome (a) Acquired neuromyotonia (a) Dermatomyositis (a) Acute necrotic myopahty (a)

(a) Neurological syndrome unassociated with known onconeural antibodies

(b) Neurological syndrome associated with onconeural antibodies but with certain particular tumours

**Table no. 2. Limbic encephalitis: clinical features and the treatment response in relation with the location of the antigens and antibodies**

	<b>Hu, Ma2, CV2/CRMP5 classical antibodies, amphiphisin (intracellular antigenes)</b>	<b>Anti-VGKC antibodies (cell membrane antigene) (21)</b>	<b>Antibodies to NR1/NR2 heteromers NMDAR (cell membrane antigen)</b>	<b>Antibodies anti other cell membrane antigens</b>
Symptoms that differ from those of the classic limbic encephalitis	Few, in accordance with the type of the antibodies	Neuromyotonia, sleeping disorders REM, epilepsy, Morvan syndrome	Psychiatric symptoms, decrease of conscience, autonomous instability, hypoventilation, dyskinesia	Rarely. The clinical picture is that of the typical limbic encephalitis
Inflammatory changes in the CSF	Frequently	Rarely or slightly	Frequently	Frequently
Interpolated synthesis of the antibodies	Frequently	Rarely	Frequently; the antibodies may be detected only in CSF	Not studied
Hyponatremia	No, with the exception of SCLC	Frequently	No	No
Initial aspect on NMR	Frequently FLAIR-hyperintensity in the medial temporal lobes (typical discoveries)	Frequently	Increased or normally ponderated FLAIR signal in the cerebral cortex, transitory meningeal intensification. In almost 25% of the cases: typical discoveries.	Typical discoveries or increased FLAIR signal in the focal cortical region
Frequently associated tumours	According to the type of antibody	Thymome or SCLC (20% of cases)	Ovary teratoma	Tumours of the tymus, Hodgkin lymphoma, SLCL, no tumour
Response to the treatment	Not frequently, with the exception of 30% of the patients with anti-Ma2 and testicular tumours	Frequently; exchange of plasma or corticoids, IVIG	Frequently; resection of the tumour, corticosteroids, plasma exchange, IVIG	Frequently; resection of the tumour, corticosteroids plasma exchange IVIG

*VGKC, voltage-gated K<sup>+</sup> channels, NMDAR, NMDA receptor, SCLC, small cells lung carcinoma, IVIG, IV immunoglobulins*

Anti-Ma2 associated antibodies mainly affect the cerebral trunk. (8) Besides the clinical picture of the limbic system, the diencephalon or the upper part of the limbic encephalitis, the patients may present

hypothalamic symptoms (15) and a syndrome characterised through the limitation of the vertical movements of sight, severe rigidity and hypokinesia. (8)

Almost 30% of the patients respond to the treatment of the primitive tumour, usually a testicular cancer and, to immunotherapy. (8) Besides anti-Ma2, other antibodies to the intracellular antigens were also reported, in association with limbic encephalitis.

Anti-N-methyl-D-aspartate antibody (NMDA) is a recently described disease that usually affects the women with ovarian teratoma. Few days after headaches or prodromic fever, most of the patients develop in stages psychiatric symptoms (agitation, hallucination) or less frequently, the short term memory is affected. (5) The intensive care and ventilation may be necessary for more weeks or months. The primitive tumour (the ovarian teratoma) is often mistaken for a physiologic or benign cyst of the ovary. The disease may also occur in men without a detectable primitive tumour. There is a large group of patients who develop classic limbic encephalitis, but whose antibodies against the membranary antigens or the known cell antigens are negative. Many of these patients have actually antibodies for unknown antigens.

### ***Paraneoplastic cerebellar degeneration***

Paraneoplastic cerebellar degeneration (PCD) is characterized by the rapid evolution of the severe pancerebellar syndrome, as a result of a large loss of Purkinje cells. PCD is especially associated to breast and ovarian tumours, small cell lung cancer and Hodgkin disease. MNR of the brain is initially normal. Exceptionally, MNR aspect may show a diffuse increase of the cerebral hemispheres with the removal of the grooves and with the diffuse captivation of the contrast substance at the level of the cerebral meninx.

Cerebral inflammation during the acute stage of PCD may also be proved with fluorodeoxyglucose upon the PET (proton emission tomography) examination, showing a cerebral metabolism that decreases visibly in time. (1, 4)

Anti-Yu antibodies associated syndrome is the most common and best characterized type of PCD. The patients usually have ovarian, breast cancer or other gynecological malignities. The patients with PCD and anti-Yo antibodies may have an undetectable tumour upon the regular screening for cancer, including PET, for years. (15) These observations suggest that the immune response is released when the tumour is still microscopic. PNS is unusual in the patients with melanoma, with the exception of the melanoma-associated retinopathy. One patient with vaginal melanoma presented PCD and opsoclonus that partially improved after the local excision of the tumour.

### ***Opsoclonus-myoclonus syndrome***

**Opsoclonus-myoclonus syndrome** is a disease of the ocular motility, characterized by irregular ocular movements, of large amplitude, continuous and in all directions. (20) Paraneoplastic opsoclonus-myoclonus may be encountered in almost 2-5% of the children with neuroblastoma. In adults, the paraneoplastic opsoclonus usually affects the women with fallopian or breast cancer

in association with the Ri antibodies, as well as the patients with small cell lung cancer without any characteristic antibody. (9) In other paraneoplastic neurological syndromes, the onconeural antibodies are of IgG1 or IgG1 and IgG3 types. The predominance of these IgG subclasses suggest that the fixation of the complement and of the cytotoxic cells – antibodies dependent – play a part in the immune pathogenesis of the paraneoplastic neurological syndromes.

### ***Paraneoplastic myelopathies***

The spinal marrow may be the predominant target of the immune-mediated attacks, associated with different paraneoplastic neurological syndrome. The patients with PEM and anti-Hu antibodies may present subacute ascending paralysis, as a result of the destruction of the motor neurons in the right cornu. (3)

Stiff Person syndrome (SPS) is a rare neurological disease, characterized by progressive muscular rigidity and spasms of the trunk and proximal parts of the limbs. Up to 70% of the patients with stiff-man syndrome have Glutamic Acid Decarboxylase Antibodies (GAD) and less frequently, anti-amphiphysin antibodies. There is recent evidence that these antibodies bring about a functional disequilibrium of the GABA interneurons from the grey substance of the spinal marrow.

The patients with paraneoplastic stiff-man syndrome have usually anti-amphiphysin antibodies. These antibodies were initially described in the women with breast cancer and stiff-man syndrome; the patients with stiff-man syndrome and anti-amphiphysin antibodies frequently present an atypical distribution of the symptoms, involving the arms, distal muscles and those of the lower limbs, usually asymmetrically, spinal myoclonus and pruritus. Recent studies show that the patient with rapid progressive myelopathy and cancer of breast or small cell lung cancer may present anti-amphiphysin or anti-CV2 (CRMP5) antibodies. The latter may also be associated to optical neuritis or retinitis, while the clinical picture is the same as at the beginning of the Devic syndrome.

### ***Lambert-Eaton myasthenic syndrome***

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of the neuromuscular junction released by the voltage-gated calcium channels (VGCC) antibodies. The predominant initial symptoms include the proximal weakness of the lower limbs, dry mouth and palpebral ptosis. Small cell lung cancer is noticed in up to 50% patients with LEMS. Today, there are no biological markers that should anticipate which patients with LEMS are paraneoplastic. There was a study that showed that 43% of the patients with LEMS and with small cell lung cancer have an antibody, called the antiglial nuclear antibody (AGNA), defined by immunoreactivity with the nuclei of the Bergman glial cells of the cerebellum. While the frequency of the antiglial nuclear antibodies was larger than the one expected in the LEMS patients with small cell lung cancer, no patient with idiopathic LEMS registered these antibodies. AGNA antigen was recently

identified as SOX1, a strong immunogenic antigen of the small lung cancer, which is also expressed at the level of the early neuroectoderm. (18)

### **Management of the paraneoplastic neurological syndromes**

The main objective of the management of a patient with a PNS is to cure the underlying cancer and to improve or stabilize the neurological disorder. The percentage of the patients whose cancer is cured is suboptimal, because of two reasons: the tumor, most frequently associated to a PNS, cannot always be treated and when it is detected, it has already invaded the regional lymphatic ganglions. (2) One of the exceptions is represented by the anti-Ma2 limbic encephalitis, where the testicular tumour is limited to testicular and may be found in a microscopic stage during the development of the PNS. (13)

The first step in the attempt to cure the cancer is to put an early diagnosis. A late diagnosis may be shortened by better understanding and knowing the clinical manifestations of the PNS and by a close collaboration with the radiologists in order to detect the primitive tumour, as well as by the use of the imagistic techniques, such as computerized tomography and combined studies with PET. (2) However, even a negative PET may not exclude the presence of a microscopic tumour. The early diagnosis of the tumour not only that it increases the possibility of a successful therapy, but it represents the best guarantee in order to improve and stabilize the paraneoplastic syndrome.

The positive effect of the treatment of the tumour was observed in the paraneoplastic opsoclonus, LEMS and PEM, associated with Hu antibodies. The effect of the immunotherapy in PNS should be taken into consideration according to the type of PNS. In LEMS, opsoclonus-myoclonus and possibly, the syndrome associated to the NMDA receptor antibodies, there is a functional neural dysfunction, rather than an irreversible one, and that is why immunotherapy is efficacious. In other PNS, there is a variable degree of irreversible neuronal damages, so that the purpose of any immunotherapy should be the stabilization rather than the improvement of the neurological syndrome. The improvement was more frequently described in the patients with limbic encephalitis associated with anti-M2 and with PCD in Hodgkin disease. In opposition with the patients with limbic encephalitis or with PCD or Hu antibodies, or with PCD and Yo antibodies, the disease rarely improves. Generally, the impact of immunotherapy on the PNS tumours is unclear, because the number of the treated patients is relatively small and the patients also receive antineoplastic treatment and the prospective studies are missing. Although, immunosuppression may theoretically exacerbate the increase of the tumour, we did not find it as a factor unfavourably prognosticated for survival. However, precaution must be taken in the use of the immunosuppressant therapies in the immune-mediated paraneoplastic syndrome, because of the fact that it may favour the increase of the tumour.

### CONCLUSIONS

Neurologists must be aware of neurological syndromes that may have a paraneoplastic origin. Detention of onconeural antibodies is crucial to make the correct diagnosis. Immunotherapy should be used, although the impact of the treatment is unclear in cases with irreversible neuronal damage.

Recent information about opsoclonus-myoclonus and about the encephalitis associated with teratomas, suggest the fact that antibodies identified in these syndromes recognize the membrane antigens and play a pathogenic part.

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