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An overview of paraneoplastic neurological syndromes – pathophysiology and clinical insight

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ABSTRACT

Paraneoplastic syndrome (PS) is a dysfunction of organs or systems, associated with neoplastic disease, but not related to the local growth of tumor, metastasis or adverse anti-cancer drugs reactions. Neurological paraneoplastic syndromes (NPSs) may affect every region of a human nervous system - both central, peripheral, and/or autonomic nervous system. The symptoms are caused by a neoplastic process in other organ or system. PNSs usually precede the development of cancer for months or even years, and can be therefore useful diagnostic markers of cancer. They present an autoimmune background associated with the response of the immune system against cancer cells. In the blood serum and cerebrospinal fluid of patients with PNS appear onconeural antibodies, reacting with tumor antigens and the brain, the spinal cord and peripheral ganglia antigens. Many authors emphasize the significance of paraneoplastic syndromes in the modern oncology. Due to this reason, the knowledge of paraneoplastic syndromes and their mechanisms is very important in the contemporary medicine. The purpose of this research review is to summarize the information about the clinical features of the most common PNSs and the pathological mechanisms of their development.

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***Keywords*:** paraneoplastic neurological syndromes, encephalitis, opsoclonus-myoclonus, dermatomyositis

List of abbreviations:

BBB – *blood-brain barrier*
DM – *dermatomyositis*
LE – *limbic encephalitis*
LEMS – *Lambert-Eaton myasthenic syndrome*
OA – *onconeural antibodies*
OMS – *opsoclonus-myoclonus syndrome*
PNS – *paraneoplastic neurological syndrome*
PS – *paraneoplastic syndrome*
SCD – *subacute cerebellar degeneration*
SCLC – *small cell lung cancer*

1. INTRODUCTION

Paraneoplastic syndrome (PS) is a dysfunction of organs or systems, associated with neoplastic disease, but not related to the local growth of tumor, metastasis or adverse anti-cancer drugs reactions. PS occurs in the areas that are not directly affected by malignant tumor (1).

Paraneoplastic neurological syndromes (PNSs) may affect every region of a human nervous system - both central, peripheral, and/or autonomic nervous system (2). The symptoms are caused by a neoplastic process in other organ or system. NPSs usually precede the development of cancer for months or even years, and can be therefore useful diagnostic markers of cancer. Studies performed on large groups of patients have confirmed the presence of PNSs before the cancer diagnosis among 80% of cases (3). Additionally, the paraneoplastic markers respond to antineoplastic therapy and usually disappear after the treatment of the underlying disease. Furthermore, they also tend to be detectable again in case of the relapsing proliferative process (4). For this reason, paraneoplastic syndromes are also a useful indicator of the response to the applied treatment and provide an information on patient prognosis.

The first description of paraneoplastic neurological syndromes comes from 1890, when the French physician M. Auche described the cases of peripheral nervous system disorders in patients with diagnosed cancer (5). Nowadays, PNSs attract the attention of specialists as important, predictive diseases for cancer or accompanying its development. The knowledge about their pathogenesis is permanently getting wider.

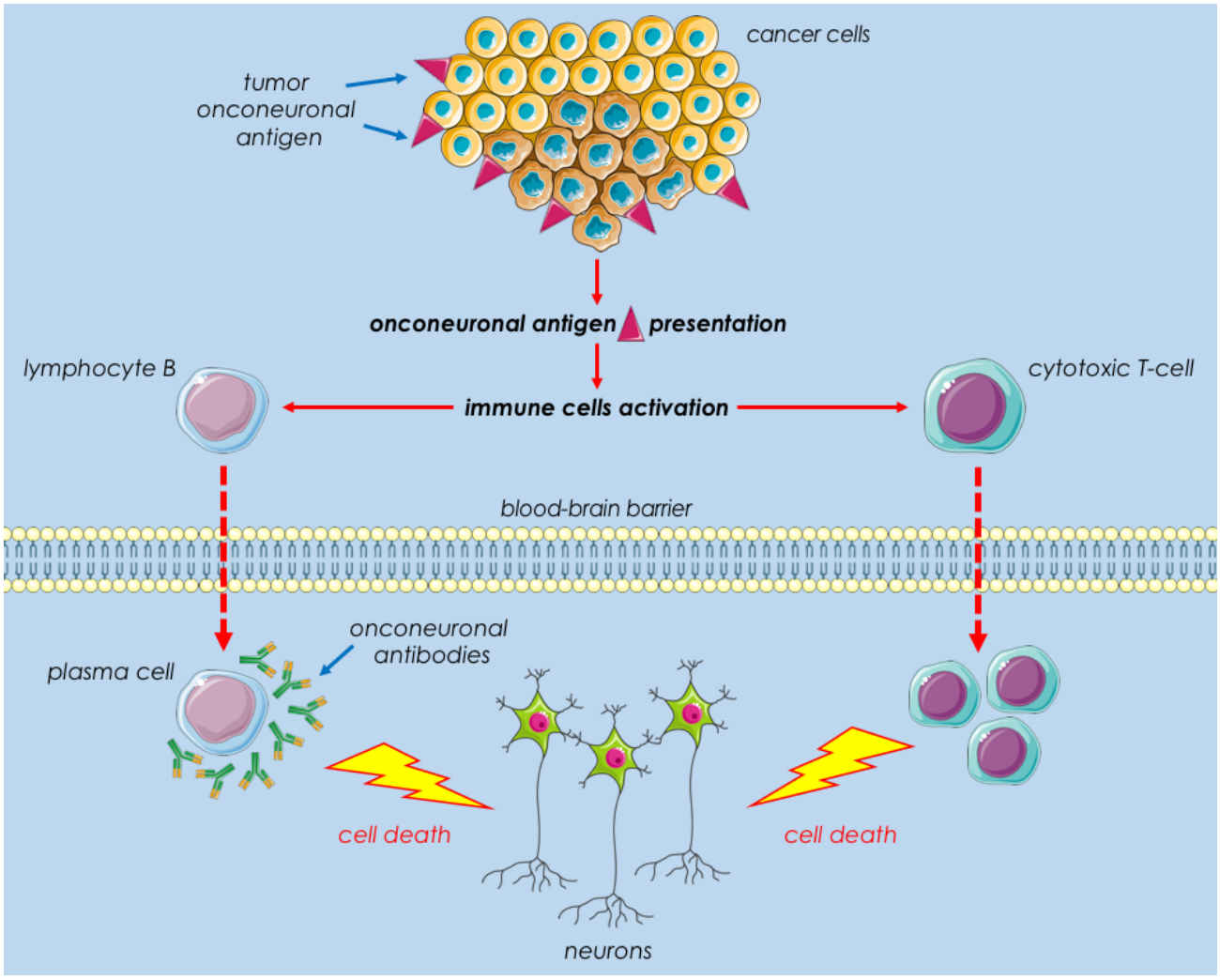
The purpose of this research review is to summarize the information about the clinical features of the most common PNSs and the pathological mechanisms of their development.

2. PATHOPHYSIOLOGY

Paraneoplastic neurological syndromes have an autoimmune background associated with the response of the immune system against cancer cells. When the body attempts to

eliminate cancer cells, the immune mechanisms are activated, what affects normal neural tissues as well (6).

On the surface of tumor cells, are expressed specific antigens, which are called *the onconeural proteins*. These antigens, which are recognized as foreign for the body, lead to the activation of the immune system (7). Activated B and T lymphocytes pass through the blood-brain barrier (BBB), recognize onconeural antigens-presenting cells and trigger a cascade of processes promoting destruction of tumor cells as well as nervous tissue (8). In the blood serum and cerebrospinal fluid of patients with PNS appear *onconeural antibodies* (OA), reacting with tumor antigens and the brain, the spinal cord and peripheral ganglia antigens (Scheme 1).



Scheme 1. The immunopathogenic mechanism of paraneoplastic neurological syndromes. Based on (9) and Servier Medical Art website, http://smart.servier.com.

Currently, onconeuronal antibodies are divided into two main categories (Table 1): well characterized and partially characterized OA strongly related to the cancer.

Table 1. The classification of onconeuronal autoantibodies. Based on (10)(11).

Well characterized onconeuronal antibodies	**Partially characterized onconeuronal antibodies**
anti-Hu (ANNA1; antineuronal nuclear antibody type 1)	**anti-VGCC** (anti P/Q type voltage-gated calcium channel antibody)
anti-Yo (PCA1; Purkinje cells cytoplasmic antibody 1)	**anti-VGKC** (anti-voltage-gated calcium channel antibody)
anti-CV2 (CRMP5; collapsing response-mediator protein 5)	**anti-Tr**
anti-Ri (ANNA2; antineuronal nuclear antibody type 2)	**ANNA3**
anti-Ma2	**PCA2**
anti-amphiphysin	**anti-Zic4**
	AGNA (anti-glial nuclear antibody)
	anti-mGluR1 (metabotropic glutamate R receptor 1)
	anti-NMDAR (N-methyl-D-aspartate receptor)

3. DIAGNOSIS OF PNS

Paraneoplastic neurological syndromes are observed with an increased incidence among oncological patients and mostly are featured by a specific proliferative process (*Table 2*) (12). For example, a patient diagnosed with myasthenia gravis should be examined for thymoma (13). Similarly, the half cases of the *Lambert-Eaton myasthenic syndrome* (LEMS) are paraneoplastic, which might be associated with small cell lung cancer (SCLC) (14). The symptoms of an *opsoclonus-myoclonus-ataxia syndrome* is an indication for immediate diagnosis towards neuroblastoma in children (15) and other solid tumors (usually SCLC) in adults (16). Some diseases known as paraneoplastic neurological syndromes more often occur without a tumor. For example, *Guillain-Barré syndrome* may be characterized as paraneoplastic accompanying (or overtaking) non-Hogdkin's lymphoma, but more frequently it is clinically isolated (17). The presence of onconeuronal antibodies is an useful tool of diagnosis of paraneoplastic neurological syndromes. These biomarkers may be found in the blood serum and/or in the cerebrospinal fluid (18). Determining the level of single antibody or their combination can help in a detection of the early stage of cancer. Many onconeuronal antibodies are found in specific PNSs, accompanying individual cancers (Table 2).

Table 2. The clinical correlation between PNSs, cancers and determined antibodies, based on (11)(19)(20).

PNS	Cancer	Antibodies
Limbic encephalitis	ovarian teratoma, SCLC, breast cancer, thymoma	*anti-Hu* *anti-Ri* *anti-CV2* *anti-amphiphysin* *anti-VGKC*
Subacute cerebellar degeneration	Breast cancer, ovarian cancer, lung cancer, Hogdkin's lymphoma	*anti-Yo* *anti-Tr* *anti-VGCC* *anti-Hu*
Opsoclonus-myoclonus syndrome	Children: neuroblastoma; adults: breast cancer, ovarian cancer, lung cancer	*anti-Ri* *anti-Hu*
Lambert-Eaton myasthenic syndrome	SCLC, prostate cancer, stomach cancer	*anti-VGCC* *anti-Hu*
Dermatomyositis	Ovarian cancer, breast cancer, lung cancer	*anti-Mi2*

The presence of onconeuronal antibodies indicates a high probability of cancer development, but it is not synonymous with its diagnosis. There is no detectable antibodies in the blood serum and cerebrospinal fluid In about 30% of patients with suspected PNS (6). Similarly, some onconeuronal autoantibodies may be presented in patients without any neurological disorders. Nevertheless, the correlation between the increased OA levels and the presence of PNS and cancer in a significant number of cases, makes onconeuronal antibodies considered to be important markers of the neoplastic process. The study of cerebrospinal fluid in patients with PNS, in addition to onconeuronal antibodies, allows also to detect other abnormalities. In the study of Psimaras et al., an inappropriate CSF was found in 93% of patients, and in this group: pleocytosis in 39%, increased protein concentration in 67% and oligoclonal bands in 63% of patients (21). The remaining procedures which are important for the diagnosis of PNS include the actions necessary for the standard recognition of neurological disorders such as: imaging, electroencephalography, nerve conduction studies, electromyography or serologies (22). Because most of the patients diagnosed with PNS will not develop cancer at the time, screening and observation for a tumor is highly recommended.

4. CLINICAL SIGNS AND SYMPTOMS

Paraneoplastic neurological syndromes can affect every part of the nervous system. Symptoms associated with PNS development may display that specific structure of a nervous

system is involved. The course of illness is usually subacute, progressive and may cause permanent loss of nervous system function.

The most common paraneoplastic neurological syndromes include (1)(4):

1. Limbic encephalitis.
2. Subacute cerebellar degeneration.
3. Opsoclonus-myoclonus.
4. Lambert-Eaton myasthenic syndrome.
5. Dermatomyositis.

4. 1. Paraneoplastic encephalitis

Limbic encephalitis (LE) was the first identified and described neurological disorder with a confirmed cancerous background (23). Currently, two types of this disease are distinguished depending on the presence of onconeuronal antibodies: paraneoplastic and idiopathic. LE syndrome is most often accompanied by an increased expression of *anti-NMDA receptor* antibodies and affects mainly women with ovarian teratoma (24). The second tumor strongly associated with LE is small-cell lung cancer. Alamowitch et al. revealed that 50% of patients with limbic encephalitis and SCLC indicated antibody-positive reaction and usually with detected presence of *anti-Hu* antibodies (25).

The histopathological image of LE is dominated by the inflammation and swelling of the limbic area: the hippocampus and amygdalae - the structures which are responsible for memory, learning and emotions (26). Therefore, the symptoms of damage of these structures are dominant in the clinical state. The intensity of symptoms depends on the severity of the disease and the patient's age. The onset of the disease is usually subacute, less often acute. Short-term memory disturbances, behavior disorders (including emotional lability), psychosis, epileptic seizures (focal or generalized with consciousness disorders) are observed. With the ongoing disease progress , they include dyskinesias, paresis and autonomic disorders, as well as respiratory failure. Among children, motor disorders and convulsions are more common than in adults (27). In the diagnosis of LE, it is necessary to perform a magnetic resonance imaging (MRI) or positron emission tomography (PET) with the use of fluorodeoxyglucose in which bilateral changes in the medial temporal lobes may be revealed. The analyses of cerebrospinal fluid show elevated levels of total protein, IgG titers and oligoclonal bands. An electroencephalographic examination may reveal changes indicating epileptic seizures. In the study carried out on a group of 23 patients with LE, an unique electrographic pattern called "extreme delta brush" was found in 30% of them. This record was associated with a more severe course of the disease requiring prolonged hospitalization (28).

4. 2. Subacute cerebellar degeneration

Subacute cerebellar degeneration (SCD) is a disorder of the nervous system that affects Purkinje cells in the cerebellar cortex (29). Purkinje cells are large, multipolar neurons responsible for the transmission and processing of information. Paraneoplastic SCD is most often associated with an increased level of *anti-Yo* antibodies (30) and occurs in women with breast or ovarian cancers (31). Sometimes SCD symptoms accompany patients diagnosed with small cell lung cancer (32), Hodgkin's lymphoma (33) or urinary bladder cancer (34).

The onset of the disease is usually severe. The symptoms include: progressive ataxia (motor dysfunction) of the trunk and limbs, nausea, dizziness, double vision. The patient's

speech is slow, indistinct and aphonic. In the course of the illness, the symptoms evolve; memory and swallowing disorders may be noticed (35).

The determination of the level of *anti-Yo* antibodies in the blood serum is of the high importance in the diagnosis of paraneoplastic SCD (36). If onconeuronal antibodies are detected, the diagnosis of ovarian cancer and breast cancer is obligatorily needed (37)(38). Approximately 50% of SCD cases are associated with above mentioned tumors.

4. 3. Opsoclonus-myoclonus syndrome

Opsoclonus-myoclonus syndrome (OMS) is a paraneoplastic disorder that appears as a result of the autoimmune process involving the nervous system. The disease is observed in 2-3% of children with neuroblastoma (39). Some studies reported also OMS connection with celiac disease (40). In adults, opsoclonus-myoclonus syndrome is very rare – usually appears as the first clinical manifestation of breast, lung or ovarian cancer (16). Furthermore, this syndrome may also be idiopathic, less likely may be a symptom of brainstem encephalitis, as well as metabolic or toxic disorders. The term "*opsoclonus*" was introduced in 1913 by a Polish neurologist – Prof. K. Orzechowski (1878-1942). In 1927 Prof. K. Orzechowski also linked the opsoclonus with myoclonus (41). The course of the disease is usually subacute. The main symptoms of the disease are opsoclonus and myoclonus. Opsoclonus syndrome is spontaneous, irregular multifactorial and conjugated with fast eye movements (42). Eye movements are characterized by high frequency (10-15 Hz), large and variable amplitude (43). Myoclonus syndrome involves an involuntary, short-lasting cramps of individual muscles or muscle groups (44). For this reason, the disease is sometimes called a syndrome of "dancing eyes" and "dancing feet" (45). Other symptoms include: lethargy, irritability, strabismus, cerebellar ataxia and aphasia (46). In the diagnosis of opsoclonus-myoclonus syndrome are used neuroimaging and laboratory tests. to exclude systemic cancer (47). The other methods as western blotting and immunohistochemistry may demonstrate the presence of onconeuronal antibodies such as: *anti-Ri*, *anti-amphiphysin*, *anti-Hu* (48).

4. 4. Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a disease characterized by a disturbance in a transmission of impulses from the nervous system to the skeletal muscles. The reason of such disorder is an inappropriate function of the calcium channels in the presynaptic membrane. In about 60% of cases it develops in people suffering from malignant tumors - most often small cell lung cancer or large intestine, although it may also occur in the course of other cancers (breast, prostate, stomach cancer) (49)(50). The disease develops usually after the age of 40, and its symptoms often precede the diagnosis of cancer (51). LEMS, similarly to other paraneoplastic neurological syndromes, has an autoimmune background. Among the clinical symptoms, weakness of proximal skeletal muscles dominates - mainly thighs and arms (*muscle fatigue*). The patient has problems with climbing stairs and raising his hands up (52). The patellar and ankle jerk reflexes are exaggerated. Others symptoms include: autonomic disorders (dry mouth, difficult swallowing, orthostatic hypotension, impotence), paresthesia, sometimes cerebellar ataxia. Symptoms of the syndrome may increase due to high temperatures, hot baths or infections (53).

Confirmation of the diagnosis is established on the basis of electromyographic examination (EMG) and neurographic examination. Complete oncological diagnosis should

be performed to detect cancer. It includes: chest computed tomography, colonoscopy, mammography in women, gynecological examination, research for prostate cancer in men.

In differential diagnosis, myasthenia gravis should be considered first of all. In the case of LEMS, the patient feels better in the morning than in the evening, and a small effort brings improvement. There can be also observed dry mouth, and rarely the bulbar palsy signs(54).

4. 5. Dermatomyositis

Dermatomyositis (DM) is an inflammatory disease, in which the changes affect especially the muscles of the shoulder and pelvis (proximal myopathy), and skin changes: erythema and edema, which are located mainly on the face and limbs. In about 50% of cases in people over 40 years of age dermatomyositis is accompanied by neoplasms of internal organs. There is an increased risk of ovarian, lung, stomach, pancreatic and Hodgkin's cancer. In a significant part of cases, dermatomyositis precedes the proliferative process, which is found later (55).

The disease usually occurs with high fever and general muscular weakness. Patients raise their hands with great effort, have a problem with getting up, squats doing and going up the stairs. Most often, the first skin symptom is bluish-red face edema (especially the orbital region and eyelids). The erythema spots and urticarial eruptions spread to the neck and neckline, forming the so-called *shawl symptom*. On the skin of the hands, over the small joints, apear flat, bluish lumps, erythema and telangiectasia - *Gottron's symptom*. There are erythematous lesions and petechiae within the nail ducts.

The skin of the hand may become hard so called "*mechanic's hand*". There is also observed an alopecia with exfoliation and calcium deposits in the subcutaneous tissue (most commonly in the area of joints). When the disease progresses, speech, swallowing and breathing disorders occur, the general condition of the patients is getting worse and more severe. The severity of muscle changes can be monitored by determining the creatine phosphokinase (CPK) level in the blood serum and using the special short time inversion recovery (STIR) technique of magnetic resonance (56).

5. TREATMENT

Treatment of paraneoplastic neurological syndromes includes (literature):

- anti-cancer therapy,
- immunotherapy,
- symptomatic treatment.

The basic way to stabilize paraneoplastic neurological syndrome is to treat the cancer as soon as possible. Such procedures include surgical excision of pathological tissues, chemotherapy and/or radiotherapy. Immunotherapy includes corticosteroids, plasma exchange and drugs, such as: azathioprine, cyclophosphamide, rituximab. The supportive therapy includes: analgesics, antiepileptics, antipsychotic, dysautonomia medications and physiotherapy (1)(6).

6. CONCLUSIONS

The immune-mediated paraneoplastic neurological syndromes are important predictive, as well as diagnostic factors for internal organ cancers. An early identification of PNS may help in the diagnosis of the tumor and choice of proper treatment. The detection of antineuronal autoantibodies indicates the necessity of oncological diagnostics. Many authors emphasize the significance of paraneoplastic syndromes in the modern oncology. As the number of patients with cancer still increases, the incidence of PNS will also confidently upsurge. Due to this reason, the knowledge of paraneoplastic syndromes and their mechanisms is very important in the contemporary medicine.

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