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Neurological Paraneoplastic Syndromes in most Common Cancers in Poland

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ABSTRACT
INTRODUCTION: Paraneoplastic Neurological Syndromes (PNS) represent a heterogeneous group of diseases associated with the presence of neoplasm. The appearance of PNS can precede cancer diagnosis. The estimated frequency amongst cancer patients is about 1%. Malignant tumors represent a serious health problem and are the second leading cause of death in Poland. The aim of this study is to collect information about PNS focusing on cancers mostly diagnosed in Polish adults.
REVIEW METHODS: The analysis was conducted based on information regarding PNS gathered from PubMed and Google Scholar within the context of selected cancers.
THE STATE OF KNOWLEDGE: PNS develop from an autoimmune reaction in which onconeural antibodies are produced. The recent classification divides PNS to high risk, indicating a likely paraneoplastic origin and intermediate risk, if this association is less evident. Diagnosis is difficult and usually relies on exclusion methods. The symptoms described are non-specific and the diagnostic process may require the involvement of various specialists. The main approaches include cancer treatment, especially tumor removal and immunotherapy, which in certain may prove to be effective.
SUMMARY: Although PNS is relatively rare, its detectability has recently increased.
Many syndromes are especially associated with lung cancer (mainly small cell carcinoma).
Breast and prostate cancers have also shown associations with certain syndromes.
They can present with nonspecific symptoms related to different organ systems.
Awareness and understanding of this phenomenon can be helpful amongst many specialists.

KEYWORDS: neurology, oncology, paraneoplastic neurological syndrome, cancer

INTRODUCTION AND PURPOSE:

Malignant tumors are a substantial and pressing issue in terms of healthcare, public welfare and economy. As the second leading cause of mortality in Poland, after cardiovascular diseases, in 2020 they contributed to 21.8% of male deaths and 20% of female deaths. [1] Cancer of Trachea, Bronchus and Lung (15%), Colorectal cancer (13.3%), Breast cancer (12.2%) and Prostate cancer (11.1%) stand for over half of all adult malignancy cases in Poland. [2]
Paraneoplastic syndromes (PS) refer to a variety of symptoms that emerge in association with neoplasms. Current estimates suggest that these symptoms occur in 8–15% of cancer patients and those numbers will likely increase as more PS cases are being diagnosed. [3] Paraneoplastic

neurological syndromes (PNS) affect approximately 1% of all cancer patients. PNS develop in approximately 80% of patients before cancer diagnosis and can be the first symptom of malignancy. [4] In view of the high incidence of cancer, rapid and accurate diagnosis is essential to predict patient prognosis and ensure effective treatment. Neuropathy is the most common clinical manifestation of paraneoplastic syndrome (PS) [5], so it is important for clinicians to be aware of the potential cause of this condition.
This article gathers information about PNS, focusing on those linked with most common cancer amongst Polish adults to raise oncological vigilance.

REVIEW METHODS:
This article gathers information from publications available on PubMed and Google Scholar and focuses on neurological paraneoplastic syndromes associated with selected common tumors. The most common cancer groups in Poland were identified using the European Cancer Information System. This group includes colon, breast and prostate cancers, as well as tracheal, bronchial and lung cancers, which together account for about half of all cancer cases in Poland.

THE STATE OF KNOWLEDGE:

Paraneoplastic Neurological Syndromes:
Paraneoplastic Neurological Syndromes (PNS) are described in the literature as a heterogeneous group of diseases that develop in response to the presence of neoplasm. Paraneoplastic Neurological Syndromes, as the name suggests, refers to a group of symptoms that result from neurological disturbances. PNS belongs to the larger category of paraneoplastic syndromes (PS), along with endocrine, cutaneous, rheumatic, hematological, renal and psychiatric ones. It is important to emphasize that these syndromes are not a direct consequence of the tumor itself, but a response to its presence.
The cause of PNS is primarily an autoimmune reaction leading to the formation of onconeural antibodies. This is the result of immunological cross-reactivity between similar proteins found in/on cancer cells and cells of the nervous system. [6] There is the following division of onconeural antibodies into: cell surface directed antibodies and intracellular directed antibodies. The presence of intracellular antigens triggers a cellular response that destroys cells of the nervous system through the action of CD8+ cytotoxic T lymphocytes.
The presence of intracellular antibodies can be considered as a potential manifestation of an ongoing cellular response. They are not directly pathogenic. Cell surface antigens mediate a humoral response in which activated B lymphocytes produce antibodies. These antibodies are potentially pathogenic. [7]
Intracellular antibodies include: ANNA-1 (Hu), ANNA-2 (Ri), PCA-1 (Yo), ANNA 3 (DACH1), Ma2 (with or without Ma1), Amphiphysin, AGNA (SOX1), Kelch-like protein 11, CRMP5 (CV2). Cell surface antibodies include mGluR1, PCA-Tr (DNER), AMPAR, GABA A, GABA B, NMDAR, and CASPR2. Detection of specific antibodies may help identify paraneoplastic syndromes, tumor types and clinical risks associated with their occurrence.
Performing the above-mentioned tests for the presence of antibodies is part of the PNS diagnosis. The materials used to detect antibodies are serum and cerebrospinal fluid (CSF). It is considered best to test both. Testing methods include Western blot, ELISA or radioimmunoprecipitation assays for intracellular antigens and transfected cell-based assays (observer-based or flow cytometry) for cell surface antibodies. [8]

However, the beginning of PNS diagnostics involves a thorough medical history, neurological examination and the exclusion of other possible causes of the given syndrome. Paraneoplastic neurological syndromes diagnoses are made through exclusion since some medical conditions may have several potential causes, with cancer being just one of them and usually a rare one. Nevertheless, this does not exempt the clinician from oncological vigilance and performing a medical history focused on cancer should be considered at the early stage of the diagnostic process.

Commonly, the first imaging test aimed at detecting tumors is a CT scan of the chest, abdomen and pelvis. Negative results do not conclusively rule out the presence of a neoplastic process. In the event of this a PET scan is recommended, along with a several-year CT scans follow-up. Other diagnostic tests aimed at detecting cancer largely depend on the suspected type and diagnostic steps should be chosen accordingly.

Search for neurological conditions includes mainly MRI of the brain and spinal cord, Electroencephalography (EEG) and Electromyography (EMG). Abnormalities in MRI often can indicate a specific paraneoplastic syndrome. There are cases and syndromes in which the MRI image is normal or becomes abnormal over time. A negative MRI result, in the presence of symptoms and other positive tests, should not deter the clinician from making a diagnosis. EEG is used when encephalitis is suspected, while EMG is performed in Lambert–Eaton myasthenic syndrome (LEMS).

The general principles of treating PNS can be divided into tumor treatment, immunotherapy and symptomatic relief. Treating the tumor, especially removing it as the source of the problem, is the best option. Especially when immunotherapy is ineffective. The success of immunotherapy varies depending on factors such as the type of present onconeural antibodies, tumor type, the type of paraneoplastic neurological syndrome and patient phenotype (age, gender). It is recognized that patients with the presence of surface antibodies generally respond well to immunotherapy, in contrast to those with intracellular-directed antibodies. The methods commonly used in immunotherapy include the administration of corticosteroids, intravenous immunoglobulin (IVIG), cyclophosphamide and plasmapheresis. [9]

In the past, PNS was classified into classical and non-classical types. This classification has been replaced by a new one, distinguishing high-risk (former classical) and intermediate-risk (former non-classical) PNS. Division is based on the clinical picture and detected onconeural antibodies. High-risk syndromes, based on epidemiological studies, have a high probability of having a paraneoplastic origin, while in intermediate-risk syndromes, this association is weaker. High-risk syndromes include Limbic Encephalitis, Encephalomyelitis, Paraneoplastic Cerebellar Degeneration, Subacute Sensory Neuronopathy, Gastrointestinal Pseudo-obstruction, Lambert Eaton Myasthenic Syndrome, Opsoclonus Myoclonus, whereas intermediate-risk syndromes include Encephalitis (extra-limbic), Brainstem Encephalitis, Morvan Syndrome, Isolated Myelopathy, Stiff Person Syndrome, Polyradiculopathy. [8] [9]

This paper follows the above division and discusses PNS associated with the selected (return to Introduction) most common cancers in the adult population in Poland.

HIGH-RISK PARANEOPLASTIC NEUROLOGICAL SYNDROMES:

Lambert Eaton myasthenic syndrome:

Lambert Eaton myasthenic syndrome (LEMS) is a rare neuromuscular disorder in 60% of cases associated with an underlying tumor. LEMS is linked to antibodies that act against P/Q-type voltage-gated calcium channels (VGCC) in presynaptic membranes. These VGCCs release

calcium, triggering the release of acetylcholine in the neuromuscular junction. In LEMS antibodies interfere with this process, reducing acetylcholine release.[10]
LEMS is characterized by progressive proximal limb weakness (that usually starts in the lower limbs and follows with involvement of the upper limbs, then distal muscles and finally the ocular and bulbar muscles, leading to difficulty walking and reduced deep tendon reflexes. Cranial nerve involvement may manifest as blurred vision, diplopia and ptosis. The autonomic nervous system can lead to dry mouth and constipation. [11]
Paraneoplastic LEMS is primarily associated with small cell lung cancer (SCLC) but can also occur with non-small cell, mixed lung carcinomas and prostate cancer. The presence of clinical features should prompt an evaluation for Lambert-Eaton myasthenic syndrome. The diagnosis of LEMS can be confirmed by the presence of P/Q-type VGCC antibodies along with electrodiagnostic studies. Antibodies against the P/Q-type VGCC detected in a radioimmunoassay are present in around 85%-95% of patients with Lambert-Eaton myasthenic syndrome, but they are not specific to LEMS. [10]
Electrophysiologic findings include decreased compound muscle action potential (CMAP) and decremental repetitive nerve stimulation (RNS) at low frequency with increment >100% at maximum voluntary contraction or high frequency. The motor weakness in LEMS can be improved with 3,4-diaminopyridine, cholinesterase inhibitors and immunosuppressive therapy (glucocorticoids, intravenous immunoglobulin (IVIG) and plasma exchange). Targeted chemotherapy for the underlying malignancy can improve the clinical course of paraneoplastic LEMS. [12]
Due to the strong association with malignancy, a diagnosis of LEMS should prompt a thorough search for underlying malignancy with initial imaging studies, such as chest CT or MRI. In the absence of initial findings, regular cancer screening should be maintained every 3 to 6 months for a minimum of 2 years.[10]

Paraneoplastic encephalomyelitis:
Paraneoplastic encephalomyelitis (PEM) is a condition that involves multiple areas of the central nervous system, impacting the brain and the spinal cord. [13] PEM induces broad neural dysfunction, with symptoms emerging from various regions like the temporal lobes, limbic areas, brainstem, cerebellum, spinal cord, dorsal root ganglia and the autonomic nervous system. Clinical presentation varies, presenting as isolated, multifocal or generalized syndromes across the central nervous system, depending on the affected neural components. The following have been singled out:

1. Paraneoplastic Limbic Encephalitis (PLE)- described further.
2. Paraneoplastic Brainstem Encephalitis / Rhombencephalitis- described further.
3. Paraneoplastic Cerebellar Degeneration- Symptoms include: dizziness, gait ataxia, oscillopsia, diplopia, dysphagia, and dysarthria.
4. Myelitis: The clinical presentation involves diverse manifestations. Subacute Sensory Neuronopathy is marked by the loss of vibration and proprioception. Paraneoplastic Motor Neuron Syndromes can manifest as spastic paresis. Another presentation entails Subacute Motor Neuronopathy, resulting in asymmetric flaccid weakness.
5. Paraneoplastic Stiff Person Syndrome- described further
6. Autonomic Dysfunction: Symptoms include orthostatic hypotension, pupillary defects, gastroparesis, intestinal disturbances, neurogenic bladder and impotence.
7. Neoplastic Neuromyelitis Optical Spectrum Disorders- Symptoms include visual loss or visual field defect.[14] [15]

Paraneoplastic encephalomyelitis is highly associated with small cell lung cancer (75% of PEM cases). Cases related to breast cancer were also registered. PEM is usually diagnosed through a process of exclusion and requires a thorough examination to rule out other causes of encephalomyelitis.

Paraneoplastic Limbic Encephalitis:

Paraneoplastic limbic encephalitis (PLE) is a rare paraneoplastic syndrome, occurring in less than 1 per 10,000 patients. However, up to 50% of these patients may experience lung cancer and almost 8% breast cancer. Another cancer associated with PLE also include prostate cancer.

Most patients with PLE exhibit antibodies such as anti-TA, anti-Hu, anti-mGluR5, anti-GABA B, anti-Ma, anti-glutamate receptor and anti-NMDA receptor.[16] Notably, in some patients, these antibodies are absent despite the presence of the disease. Anti-Hu antibodies are the most common, specifically associated with small cell lung cancer. Anti-Ma2 antibodies are associated with testicular cancer.[12]

The affected area in PLE is primarily the medial temporal lobe. Common symptoms include behavioral changes, irritability, short-term memory loss, cognitive dysfunction with subacute onset, hallucinations, convulsions and, less frequently, hypothalamic symptoms such as endocrine disorders or hypothermia. Early psychiatric symptoms often lead to psychiatric treatment before an accurate diagnosis is made.[4][16]

Diagnosis is challenging and is primarily exclusionary. Various tests, including blood tests for monoclonal antibodies, EEG examination revealing epileptic activities in the temporal lobe, and MRI imaging showing hyperintense signals in the temporal lobe, contribute to the diagnostic process.[16]

The primary treatment for PLE involves addressing the underlying cause, such as chemotherapy or surgical tumor removal. Supportive treatments encompass high doses of corticosteroids, immunosuppressive drugs like rituximab and plasma exchange.[4][16]

Limbic encephalitis is not always a paraneoplastic syndrome; it can also be associated with infections or autoimmune diseases such as type 1 diabetes or systemic sclerosis.[16]

Opsoclonus-myoclonus syndrome (OMS):

Opsoclonus-myoclonus syndrome (OMS) is a paraneoplastic disease primarily associated with small cell lung cancer and occurs in breast cancer patients.[11] [12]

Beyond its association with cancer, OMS can also manifest as an immune-mediated post-infectious process. [11] Onconeural antibodies including ANNA2 (anti-Ri), ANNA1 (anti-Hu), Ma2, CRMP5 (CV2), and NMDA-R antibodies were identified in both plasma and cerebrospinal fluid (CSF) of patients with paraneoplastic OMS. [7] Anti-Ri antibodies, most common in breast cancer cases, target the enzyme glutamate decarboxylase, which converts glutamate to GABA. This targeted attack causes cerebellar degeneration and subsequent ataxia.

OMS is commonly referred to as “dancing eye syndrome” and is manifested by spontaneous, arrhythmic, multidirectional, irregular, high-amplitude eye movements.

Associated myoclonus can affect the head, trunk and limbs. Clinical manifestations may include cerebellar ataxia and encephalopathy (which in some cases, especially in the elderly, progresses to coma). [7][11]

The clinical diagnosis of OMS is based on the recognition of the characteristic features of opsoclonus. Accurate diagnosis and appropriate treatment of the underlying cancer associated with OMS provides an opportunity to prevent further progression of the disease and allow partial or complete neurological recovery. Symptomatic treatment of OMS includes medications such as

clonazepam, gabapentin, and baclofen. [7] Little improvement is observed, especially when using immunomodulatory drugs such as steroids, IVIG and plasmapheresis. [12]

Paraneoplastic cerebellar degeneration (PCD):

Paraneoplastic cerebellar degeneration is caused by the destruction of cerebellar Purkinje cells by onconeural antibodies, which are produced in response to the presence of cancer. This process contributes to degeneration and dysfunction of the cerebellum. [12][17]

The Anti-Yo antibody is the most frequently detected among PCD patients, which is particularly associated with breast cancer and gynecological cancers. Other antibodies found in PCD are anti-Hu (associated mainly with SCLC and prostate cancer), anti-Ri, anti-Tr, anti-VGCC, anti-Ma, anti-CRMP5 and anti-mGluR. [17]

The onset of PCD symptoms may precede the diagnosis of cancer by several months or even years [17]

Patients with PCD come to the doctor with symptoms of subacute cerebellar syndrome such as double vision, unsteady gait, ataxia, dizziness, vomiting and difficulty with fine hand movements. Symptoms of brain stem damage such as nystagmus, dysarthria and dysphagia were also observed in some patients.[4] [17] Patients may also experience other extra-cerebellar symptoms such as increased peripheral pain, muscular weakness and abnormal reflexes [12]

A well-collected history and differential diagnosis play a key role in the diagnosis of PCD. A patient with cerebellar ataxia and a family history of cancer should raise the doctor's oncological vigilance.

Imaging studies such as CT and MRI should be performed to rule out the most common causes of cerebellar syndrome such as stroke and space-occupying lesions. In the initial stages of PCD, imaging tests may show no abnormalities and only show cerebellar atrophy as the disease progresses.

Laboratory tests should also be performed to determine the above-mentioned antibodies, the presence of which may help in making an appropriate diagnosis.

The condition for effective treatment of PCD is the diagnosis and treatment of the tumor responsible for the syndrome. Immunotherapy (systemic corticosteroids, intravenous immunoglobulins, plasma exchange, tacrolimus, cyclophosphamide and rituximab) may also be used in the treatment, but the response to this treatment is not always satisfactory [12][17]

INTERMEDIATE-RISK PARANEOPLASTIC NEUROLOGICAL SYNDROMES:

Stiff Person Syndrome:

Stiff person syndrome (SPS) is a rare immune-related disease characterized by progressive muscle stiffness and painful contractions triggered by external stimuli. Paraneoplastic variants of the disease account for 5–10% of all cases and are primarily associated with adenocarcinoma of the breast, followed by adenocarcinoma of the colon, small cell lung cancer (SCLC) and other malignancies [18].

The underlying cause of SPS is B cell-mediated autoimmune inflammation that affects various components of GABAergic inhibitory neurons and their synapses. Autoantibodies generated against antigens involved in GABA synthesis and release interfere with the proper functioning of major inhibitory pathways in the central nervous system (CNS) [18]. Autoantibodies observed in patients with paraneoplastic SPS include anti-amphiphysin antibodies (associated with breast cancer and SCLC), anti-DPPX, anti-GAD65, anti-gephyrin and anti-glycine receptor antibodies [7].

Classic SPS usually begins with muscle stiffness in the trunk and extends to the proximal parts of the extremities. It involves sudden, painful muscle contractions triggered by tactile, auditory, visual stimuli, or intense emotions. Commonly associated psychiatric disorders such as agoraphobia, depression, and anticipatory anxiety can be misdiagnosed as functional neurological disorders or primary psychiatric disorders. There is evidence that neoplastic SPS manifests as more pronounced stiffness of the neck and upper extremities. [18]
Diagnosis of paraneoplastic SPS is based on the identification of a characteristic clinical profile upon neurological examination, autoantibodies (mainly amphiphysin and gephyrin) and detection of the primary tumor. Electromyographic (EMG) studies reveal sustained activity of motor units of agonist and antagonist muscles) [18].
Treatment of paraneoplastic SPS focuses on addressing underlying cancer. Symptom relief includes muscle relaxants such as benzodiazepines, baclofen, tizanidine, and botulinum toxin injections to relieve muscle spasms. Immunotherapy may also be considered [7].

Polyradiculopathy:
Paraneoplastic Polyradiculopathy is characterized by the destruction of multiple nerve roots and proximal nerves, leading to neurological symptoms such as pain, muscle weakness and loss of sensation.
The onconeural antibodies most frequently associated with paraneoplastic polyradiculoneuropathy include CRMP5 (commonly linked to Small Cell Lung Cancer - SCLC), ANNA1 (anti-Hu), Amphiphysin (associated with breast cancer or SCLC) and PCA2 [7][8].
Neuropathic pain, painful weakness and sensory disturbances are the primary symptoms of paraneoplastic polyradiculoneuropathy. In cases related to CRMP5 antibodies a subacute, painful, asymmetric neuropathy with weakness in both proximal and distal limbs is observed, whereas the presence of Amphiphysin IgG antibodies manifests with symmetrical axonal polyradiculopathy [7] [8].
In diagnostics, alongside the patient's clinical presentation, the identification of relevant onconeural antibodies is crucial. In certain cases, MRI of the spine or lumbar plexus may reveal T2 hyperintensity or post-contrast enhancement of nerve roots and plexuses [9].

Subacute Sensory Neuronopathy:
Subacute sensory neuropathy (SSN) is a result of inflammation of the dorsal root ganglion and often neuronal degeneration. In clinical presentation SSN is acute or subacute, mainly asymmetric and primarily affects the upper limbs. Early symptoms include vibration and proprioceptive disturbances. Over time burning pain along with further sensory disturbances develop. Movement disorders may occur, leading to ataxia and significant limitations in function.
SNN serves as a clinical indicator and should prompt increased vigilance by medical professionals, especially since small cell lung cancer is most associated with this syndrome. Electrophysiological studies indicate that sensory responses may be absent and disturbances in motor responses may be minimal. Detection of onconeural antibodies such as anti-Hu and Amphiphysin can help identify the cause of paraneoplastic symptoms. [8] [19]
Treatment of subacute sensory neuropathy includes both causative and symptomatic treatments. Causative interventions include tumor resection and immunomodulation, but available data do not conclusively support their efficacy.[19] Timely initiation of corticosteroid therapy may contribute to improved sensory perception. [13] Symptomatic treatments for neuropathic pain include active ingredients such as gabapentin, pregabalin and tricyclic antidepressants. However,

optimal symptom relief primarily depends on effective treatment of the underlying neoplastic disease. [8]

Gastrointestinal pseudo-obstruction:

Gastrointestinal pseudo-obstruction is a term referring to disorder of the autonomic nervous system, presenting symptoms mirroring gastrointestinal mechanic obstruction without detectable cause. Antibodies anti-Hu help to identify paraneoplastic origin, often associated with small cell lung cancer and in some cases with breast cancer. Symptoms include abdominal distension, cramping, nausea, vomiting, and weight loss.

In addition to symptoms related to the gastrointestinal system other dysregulations of the autonomic system may be observed, such as orthostatic hypotension, mydriasis, heat intolerance due to anhidrosis, erectile dysfunction and urinary retention.[8]

Brainstem encephalitis/Rhombencephalitis:

The brainstem consists of the medulla oblongata, pons, mesencephalon and its inflammation can affect any of those parts. The rhombencephalon consists of the medulla oblongata, pons and cerebellum. Despite different anatomical components, the terms 'Brainstem encephalitis' and 'Rhombencephalitis' are often used interchangeably. [20] A paraneoplastic origin represents one among many potential etiologies and it is considered a rare one. Malignancies associated with brainstem encephalitis are lung and breast cancer.

Antibodies anti-Hu, anti-Ri, and anti-Ma2, Anti-NMDA have been linked with the syndrome. The type of detected antibodies appears to determine the clinical phenotype and prevalence of involvement in specific areas. [21][22]

Brainstem encephalitis with anti-Hu antibody affects mainly the medulla, causing dysarthria dysphagia and central hypoventilation. Anti-Ma2 antibody is known to impact mesencephalon, presenting as vertical gaze palsy syndrome. Opsoclonus-myoclonus syndrome and trunk ataxia are linked with anti-Ri antibodies. Anti-NMDA receptor antibody presence manifests as autonomic dysfunction, seizures, movement disorders and psychiatric symptoms. [20][23] Autonomic dysfunction may manifest through the following symptoms: hyperthermia, hypersalivation, hypotension, hypertension, tachycardia, bradycardia, urinary incontinence and erectile dysfunction. [24][25]

Isolated myelopathy:

Isolated myelopathy is a rare neurological paraneoplastic syndrome associated with the presence of small cell carcinoma and breast adenocarcinoma. [26]

Onconeural antibodies such as CRMP-5, Amphiphysin, ANNA-1 and neuronal intermediate filaments can be detected during the diagnostic process, aiding in the delivery of a diagnosis for Isolated Paraneoplastic Myelopathy (IPM). It is possible not to detect onconeural antibodies and still make a diagnosis of isolated paraneoplastic myelopathy (IPM) when MRI findings, exclusion of other causes and clinical presentation indicate such. MRI findings indicate symmetric, longitudinally extensive tract or gray matter-specific abnormalities. Symptoms include motor weakness, bowel or bladder disorders and Posterior Cord Syndrome (PCS). [27] [28]

PCS manifests as a loss of proprioception and vibratory sensation. [29][30][31]

Table 1. Paraneoplastic Neurological Syndrome, clinical presentation and the specialist who may encounter the disease in clinical practice (excluding General Practitioner)

Paraneoplastic Neurological Syndrome	Clinical presentation*	Specialist
Lambert-Eaton myasthenic syndrome	Muscle weakness, difficulty walking, blurred vision, diplopia, autonomic dysfunction**	Neurologist Ophtalmologist Cardiologist Urologist
Opsoclonus myoclonus syndrome	Opsoclonus eye movement, myoclonus of the trunk, head and extremities, ataxia	Neurologist Ophtalmologist
Limbic encephalitis	Behavioral changes, short-term memory loss, neuropsychiatric symptoms, seizures	Psychiatrist Neurologist
Cerebellar degeneration	Unsteady gait, ataxia, double vision, dysarthria, dysphagia	Neurologist Ophtalmologist
Subacute sensory neuronopathy	Asymmetric numbness, sensory impairments, neuropathic pain, sensory ataxia	Neurologist
Gastrointestinal pseudo-obstruction	Abdominal distention, cramping, vomiting, weight loss autonomic dysfunction**	Gastroenterologist Neurologist Surgeon Cardiologist Urologist
Stiff person syndrome	Muscle stiffness, painful muscle spasm triggered by external stimulus, psychiatric disorders	Neurologist Psychiatrist
Brainstem encephalitis	Vertical gaze palsy syndrome, trunk ataxia, dysphagia, autonomic dysfunction**, psychiatric symptoms	Neurologist Psychiatrist Cardiologist Urologist
Poliradiculopathy	Asymmetric weakness, sensory disturbances, neuropathic pain	Neurologist Orthopedist
Isolated myelopathy	Loss of proprioception and vibratory sensation, motor weakness, bowel or bladder disorders	Neurologist Urologist Gastroenterologist

*Symptoms may not necessarily co-occur; some may be absent.
**Autonomic dysfunction may encompass hyperthermia, hypersalivation, hypotension, hypertension, tachycardia, bradycardia, urinary incontinence, erectile dysfunction.

Conclusions

Paraneoplastic neurological syndromes are a relatively rare condition. However, up to 80% of PNS occur before the official cancer diagnosis. Therefore, the significance of early detection is

gaining importance. The accurate diagnosis is bringing patients closer to receiving timely and appropriate treatment.
Most PNS are associated with lung cancer, especially SCLC. Although, other common cancers in Poland such as breast cancer and prostate cancer are also linked to some PNS. In literature colon cancer is mentioned in the context of Stiff Person Syndrome.
The diagnostic foundation for paraneoplastic neurological syndromes lies in a profound understanding of the clinical presentation of each syndrome, coupled with a comprehensive patient interview and neurological examination. Given the nonspecific nature of many clinical manifestations, patients often traverse various medical specialties in pursuit of an accurate diagnosis (refer to Table 1). Hence, it is imperative that every medical practitioner possesses the knowledge of key diagnostic indicators and the appropriate diagnostic pathways when presented with patient concerns aligning with paraneoplastic neurological syndromes.
Diagnosing PNS is frequently intricate and relies on a process of exclusion; however, increasing awareness among healthcare professionals has contributed to enhanced PNS detection and holds the potential for further advancement.

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