Paraneoplastic neurologic syndrome: A practical approach

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Abstract

Paraneoplastic neurological syndromes (PNS) are rare disorders associated with cancer, not caused by direct invasion, metastasis or consequences of treatment. They are usually autoimmune in nature. Often, PNS precedes the manifestations of cancer. Onconeural antibodies are important in the diagnosis and management of these disorders. These antibodies are specific for the malignancy rather than for a particular neurological syndrome. Often, there are different antibodies associated with the same syndrome. Multiple antibodies are also known to coexist in a given patient with malignancy. While investigating a patient for suspected PNS, the entire gamut of onconeural antibodies should be investigated so as not to miss the diagnosis. In 30–40% of the cases, PNS can occur without antibodies. Investigations for identifying the underlying cancer can be directed by the antibody panel. If conventional screening for cancer is negative, a positron emission scanning/computed tomography scan can be useful. Patients need follow-up surveillance for cancer if not detected in the first instance. Cancer detection and treatment, immunotherapy and supportive care are important components of treatment of PNS. Immunotherapy is very effective in PNS associated with cell membrane-associated antibodies like voltage-gated potassium channel complex, NMDA receptor antibodies and voltage-gated calcium channel antibodies. Immunotherapy includes steroids, IVIgG, plasmaphereis, cytotoxic medications and rituximab. Supportive therapy includes symptomatic treatment with antiepileptic and analgesic medications, physiotherapy, speech therapy and occupational therapy. PNS can mimic any neurologic syndrome. A high index of clinical suspicion is important for early diagnosis and prompt management and better outcome.

Key Words

Immunotherapy, onconeural antibodies, paraneoplastic neurological syndrome, paraneoplastic antibodies

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Introduction

Paraneoplastic neurological syndromes (PNS) are rare, but are potentially treatable. These disorders are associated with cancer, but are not caused by the direct tumor invasion, metastasis or consequences of treatment.[1] They can affect any area of the nervous system, including the central, peripheral and autonomic nervous system. Although the system involvement is often multifocal, like encephalomyelitis, it can involve a single system, e.g. cerebellar degeneration. Mainly, the PNS precede or follow the cancer diagnosis, although, in some cases, the primary cancer is not found even at autopsy.[2]

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The first description of PNS was in the 19th century by a French physician M Auche` who described the peripheral nervous system involvement in cancer patients in 1890.[3] The first antibody described was PCA-1 (Purkinje Cell Antibody 1), by Greenlee and Brashear in 1983, in two patients with ovarian carcinoma and paraneoplastic cerebellar degeneration.[4] More syndromes and antibodies have been subsequently described and the list of the syndromes and antibodies continue to increase day by day.

Pathophysiology

PNS are mainly autoimmune.[1] When the body tries to eliminate tumor cells, it launches an immune response, and this response can target normal neural tissues.[5] This could be mediated by antibodies or by T-cells. Thus, most of the PNS reflect a nervous system-specific autoimmune attack initiated by onconeural antigens released to the peripheral lymphoid tissue from an unsuspected primary or recurrent neoplasm.[2] Frequently, a cerebrospinal fluid (CSF) study in these patients reveals lymphocytic pleocytosis, elevated protein, increased IgG synthesis and oligoclonal bands, supporting the immunological pathology. In a recent European study, abnormal CSF was

found in 93% of the cases; pleocytosis in 39%, elevated protein in 67% and oligoclonal bands (OCB) in 63%. OCBs were the only abnormality in 10%.[6] Antibodies targeted against an accessible membrane target is directly responsible for the disease, as in the case of acetyl choline receptor (AChR) antibodies in myasthenia gravis, P/Q type of voltage-gated calcium channels (VGCC) in Lambert Eaton Myasthenic syndrome (LEMS) and encephalitis associated with anti-NMDA receptor antibodies. It has been documented that tumor outcome is better among patients with paraneoplastic syndromes.[7] Often, the cancer is asymptomatic at the time of presentation with neurological syndrome. Some of the paraneoplastic antibodies are specifically associated with cancer and some are not.

Incidence and prevalence

The exact incidence and prevalence of these disorders are unknown. PNS are a rare clinical condition. The prevalence of these disorders varies from cancer to cancer. For example, PNS can occur in 2–3% of the patients with neuroblastoma or small cell lung carcinoma (SCLC) and in 30–50% of the patients with thymoma and sclerotic myeloma. Overall, it is estimated that 0.5–1% of all patients with cancer have clinically disabling PNS.[1]

Clinical features

PNS can affect any region of the nervous system. PNS can present with multiple clinical manifestations like encephalitis, autonomic failure, peripheral neuropathy, cerebellar ataxia, visual complains and many others. There can be multiple antibodies in a patient.[5] Table 1 gives the common classical paraneoplastic syndromes with clinical features and investigations.[8] Based on the evidence accumulated over the last two decades, recognition of a classical neurologic syndrome associated with single antibody is an exception rather than a rule.[2] Usually, the onset is subacute. In approximately 60% of the cases, PNS precedes tumor [Table 1].[1]

Clues to diagnosis

History or family history of cancer should alert the clinician regarding this diagnostic possibility. Medical history or family history of autoimmune diseases can be a clue to paraneoplastic neurologic autoimmunity. Subacute presentation and multiple-level involvement of neuraxis is common. The diagnosis of paraneoplastic disorder should be considered in a subacute onset and insidiously progressive neurologic condition where no clear alternate diagnosis is possible [Table 2].

Nomenclature of antibodies

Autoantibodies are classified as nuclear, cytoplasmic and cell membrane based on the predominant location of reactivity to the nervous tissue. The nomenclatures used by different groups vary. Lennon[9] proposed the generic nomenclature, which is based on immune-staining characteristics (nuclear or cytoplasmic) and chronological order of discovery (like ANNA 1, 2, 3). Similar naming was used by the groups who described the first antibody – anti-Purkinje cell and antineuronal nuclear antibody. Later, other names like Hu and Yo were introduced.[2]

Diagnosis

Early diagnosis and treatment is important because any delay can result in rapid progression and irreversible neurological damage. Diagnosing PNS is often difficult. One of the reasons for the difficulty in diagnosis is presentation of the PNS before the malignancy becomes clinically overt. Other reasons are the absence of a particular clinical pattern and absence of imaging and laboratory abnormalities that are specific for PNS. Biopsies are invasive, difficult and nonspecific. A combination of clinical

Table 1: Clinical syndromes[8]

Syndrome	Clinical feature	Investigations
Classical syndromes		
Paraneoplastic encephalomyelitis (PEM)	Subacute involvement of more than one area of the CNS – includes cortical, limbic or brainstem encephalitis, cerebellar dysfunction, myelitis	MRI of the relevant part. CSF-pleocytosis, elevated protein and OCB
Limbic encephalitis (LE)	Memory problems, seizures, mood and sleep abnormalities	MRI brain T2/FLAIR HI involving limbic structure. Abnormal CSF as above, EEG epileptiform abnormality/focal slowing
Paraneoplastic cerebellar degeneration (PCD)	Severe pan cerebellar ataxia developing in less than 12 weeks, onset appendicular	Initial MRI brain usually normal. Later cerebellar atrophy
Opsoclonus myoclonus	Involuntary chaotic saccades in all directions of gaze, associated with myoclonus and ataxia frequently	MRI brain usually normal. EMG diagnosis of myoclonus
Chronic gastrointestinal pseudoobstruction	Subacute progressive nausea, vomiting, abdominal distension, pain and constipation	GI motility study and autonomic reflex screen, thermoregulatory sweat test for associated autonomic dysfunction
Subacute sensory neuronopathy	Numbness and pain onset in upper extremity, asymmetric. Progression in less than 12 weeks.	NCS-absent or reduced SNAPs, MRI spine enhancing nerve roots. Abnormal CSF as mentioned above.
Lambert eaton myasthenic syndrome (LEMS)	Proximal weakness with ocular and bulbar involvement. Hypoactive DTRs and mild dysautonomia helps clinical differentiation from myasthenia gravis (MG)	EMG-incremental response on repetitive stimulation

CSF = Cerebro spinal fluid; DTR = Deep tendon reflex; EEG = Electroencephalography; EMG = Electromyography; FLAIR = Fluid attenuation inversion recovery; GI = Gastrointestinal; HI = Hyperintensity; MRI = Magnetic resonance imaging; OCB = Oligoclonal band; SNAP = Sensory nerve action potential; NCS = Nerve conduction study

Table 2: Neurological manifestations of paraneoplastic syndromes at different levels of neuraxis[2]

Topography	Syndrome	Antibody
Cerebral cortex	Limbic encephalitis	VGKC-related proteins, CRMP-5, AGNA-1, ANNA-1, ANNA-3, PCA-2, Ma2
	Encephalopathy	ANNA-1,2,3, PCA-2, amphiphysin, AGNA-1 CRMP-5, ganglionic Ach R, VGCC (P/Q or N), striational
Diencephalon	Hypothalamic dysfunction	Ma2, ANNA-1
Basal ganglia	Chorea	CRMP-5
	Hemi-ballismus	
	Parkinsonism	Ma
	Myoclonus	VGKC-related proteins
Cerebellum	Cerebellar ataxia	PCA-1,2,Tr, CRMP-5, AGNA-1, ANNA1,2,3 VGCC P/Q>N, GAD65, Zic4, mGluR1
Brainstem	Brainstem encephalitis	ANNA 1,2,3, PCA-2, Ma2 CRMP-5, AGNA-1, VGCC
	Opsoclonus/myoclonus	ANNA-1,2
	Stiff person syndrome	Amphiphysin
Cranial nerves	Bulbar motor neuropathies	CRMP-5, ANNA-1, PCA-2
	Optic neuropathy	
	Hearing loss	
	Retinopathy	CRMP-5, recoverin
Spinal cord	Myelopathy	CRMP-5, VGCC, amphiphysin, ganglionic AchR, VGKC
	Transverse myelitis Myoclonus	ANNA-1,2
Peripheral somatic nerves and ganglia	Sensory neuronopathy	ANNA-1, CRMP-5, ganglionic AchR Amphiphysin, VGKC, paraproteins
	Sensory motor neuropathies	
	Motor neuropathy	PCA-1, PCA-2
	Brachial plexopathy	
	Hyperexcitability syndromes	Ganglionic AChR, VGKC CRMP-5, muscle AChR
Autonomic and enteric nervous system	Dysautonomia	Ganglionic AChR, VGCC (P/Q>N type), CRMP-5, ANNA-1
	GI dysmotilities	ANNA-1, striational, VGKC, muscle AChR, GAD65
Neuromuscular junction	Lambert eaton syndrome	VGCC (P/Q>N type), muscle AChR, striational, ganglionic AChR, AGNA-1.
	Myasthenia gravis	Muscle AChR, striational, ganglionic AChR, VGKC
Muscle	Polymyositis/dematomyositis	Anti Jo

VGKC = Voltage gated potassium channel; CRMP = Collapsin response-mediated protein; AGNA = Anti glial nuclear antibody; PCA = Purkinje cell antibody; VGCC = Voltage-gated calcium channels

and laboratory evaluations has to be deployed to reach diagnosis early. Treatment of underlying cancer is important in the treatment of the neurological condition. High index of clinical suspicion is essential to achieve this goal. Past or family history of cancer is important in this regard. Presence of systemic symptoms like anorexia, weight loss, fever, fatigue and dysguesia are all important nonneurological clues. CSF often exhibit nonspecific abnormalities such as mild to moderate lymphocytic pleocytosis, elevated protein and OCBs [Tables 4 and 5].

Onconeuronal antibodies are helpful for the diagnosis [Table 3]. Presence of these autoantibodies, alone or in combination, helps to detect the tumor as they are more tumor specific than for neurological syndrome. This can guide the search for the primary cancer. These antibodies establish the autoimmune nature of the disease, helping the clinician to differentiate the new neurological symptoms of PNS from treatment related-complications like toxic neuropathies, metastasis or infiltration. They are of help in detecting the recurrence of the disease in already seropositive patients.

The limitations for the paraneoplastic antibody evaluation are that only 60–70% will have detectable antibodies and that they can be seen in patients without PNS. In general, it is almost always preferable to look for the entire range of antibodies than for one or two specific ones. This is because the same clinical syndrome is associated with multiple antibodies.[5] The practice of ordering a single antibody can result in missing the potential cases. Also, there could be multiple antibodies, which predict the type of cancer better than the presence of a single antibody [Figure 1].For example, a bundle of positive antibodies – CRMP-5 IgG, antistriational muscle antibody, anti-AChR binding and modulating, voltage gated potassium channel antibodies (VGKC) in a given patient, almost always indicates presence of a thymoma while if CRMP-5 IgG alone is detected, multiple cancers have to be looked for. CSF antibody testing is encouraged along with serum testing as there are occasions where the serum is negative and CSF has been positive.

Table 3: Oncological associations of paraneoplastic antibodies[2,14]

Antibody	Neoplasm predicted by autoantibody	Neoplasm (%) /Frequency of coexisting antibody (%)	Clinical features
Nuclear antibodies			
Anti neuronal neuclear antibody -1 (ANNA-1)(Anti Hu)[15]	Small cell lung cancer (SCLC), neuroblastoma, thymoma	81/43	PEM-limbic, cortical, brainstem encephalitis, PCD, Myelitis, PSN, autonomic dysfunction
ANNA-2(Anti Ri)[16]	Lung carcinoma, breast carcinoma	86/73	brainstem encephalitis, opsoclonus-myoclonus, PCD,
ANNA-3[17]	Lung carcinoma, upper airway carcinoma	90/30	Sensori/sensorimotor neuropathy, cerebllar ataxia, myelopathy, brainstem and limbic encephalopathy
Anti glial nuclear antibody (AGNA-1)[2,18]	SCLC	90/50	LEMS, PCD, Sensory neuronopathy, limbic encephalitis, sensory motor neuropathy
Anti Ma2[19]	Germ cell tumor of testis, Lung, GIT, breast, NHL,	unknown	Cerebellar\ brainstem syndrome Limbic encephalitis. Narcolepsy like, cataplexy, hypnogogic hallucination
Zic 4[20]	SCLC	92/27	Limbic encephalitis> Cerebellar\ brainstem syndrome
Cytoplasmic antibodies			
Purkinje cell cytoplasmic antibody (PCA)-1[21]	Ovarian, fallopian, endometrial and breast carcinoma	90/9	PCD
PCA-2[22]	SCLC	80/63	Brainstem/limbic encephalitis, PCD, LEMS, motor neuronopathy
PCA-Tr[23]	Hodgkin's lymphoma	90\ Unknown	PCD, limbic encephalopathy
Amphiphysin[24]	Breast carcinoma lung carcinoma	80/38	Stiff-man syndrome, PEM
CRMP-5[25,26] (collapsin response-mediated protein)	SCLC, thymoma, thyroid, renal carcinoma	80/57	PEM, PCD, chorea, optic neuropathy, myelopathy and peripheral neuropathy
Striational (sarcomeric proteins)[2]	SCLC, thymoma, breast carcinoma	Unknown	Myasthenia gravis
Cell membrane antibodies			
Voltage gated calcium channel (VGCC) N[27]	Lung, breast, ovarian carcinoma	Unknown	LEMS, cerebellar degeneration
VGCC P/Q[27]	SCLC	Unknown	LEMS, cerebellar degeneration
AChR, muscle[28]	Thymoma, SCLC	Unknown	Myasthenia gravis
AChR, ganglionic[29]	Thymoma, SCLC	Unknown	Autonomic neuropathy
Voltage gated potassium channel (VGKC) related protein[30,31,32,33]	Thymoma, SCLC	Unknown	Limbic encephalitis, Moorvan's syndrome, PCD, GI dysmotility, parkinsonism, tremor, chorea, ssensory motor neuropathy, hyponatremis, dyssomnia and hyperphagia
NMDA receptor[34, 35,36]	Ovarian terratoma	59%/unknown	Psychiatric features and memory loss, orofacial dyskinesia, choreoathetoid movements, abnormal posturing or increased tone, catatonic state and central hypoventilation
AMPA receptor[37]	SCLC, thymoma, breast	Unknown	Limbic encephalitis, atypical psychosis
GABA B receptor[38]	SCLC	Unknown	Limbic encephalitis
Glycine receptor[39]	Lung cancer	Unknown	Progressive encephalomyelitis with rigidity and myoclonus (PERM)
mGluR1[40]	Hodgkin's lymphoma	Unknown	PCD

SCLC = Small cell lung cancer; VGCC = Voltage-gated calcium channels; CRMP = Collapsin response-mediated protein; PCD = Paraneoplastic cerebellar degeneration; PEM = Paraneoplastic encephalomyelitis

In PNS, 15% of the patients can have an unrelated additional neoplasm.[2] Therefore, if there is an obvious neoplasm, but not the one predicted by the onconeural antibodies, search should be continued for the tumor that is predicted by the antibodies. Usually, tumor is in a limited stage and needs extensive imaging for detection. Positron emission tomography (PET)/computed tomography (CT) is useful when the cancer is not detected by any other imaging modality. In 39% of the cases, tumors were detected with PET/CT when other modalities failed to detect it.[10] Mammograms are very useful, especially when PCA-1, ANNA-2 and amphiphysin antibodies are positive. Transvaginal ultrasound is an important screen for ovarian and Mullerian cancers. Even the small or suspicious abnormalities have to be pursued diligently in the presence of a positive antibody and PNS. Every attempt should be made to pursue tissue diagnosis. Even if the patient is tumor free in the initial evaluation, he/she has to be followed-up

Table 4: Clinical and laboratory clues for paraneoplastic neurological syndromes (other than onconeural antibodies)

Paraneoplastic syndromes can present with any neurological manifestations The following features may point towards paraneoplastic etiology:

- History of smoking, history or family history of cancer, age>50 years, history of systemic autoimmunity or marker's systemic autoimmunity.
- Subacute onset , multifocal involvement.
- Neurologic syndromes unexplained by other causes.
- Inflammatory CSF, elevated CSF protein or OCBs alone and MRI findings compatible with paraneoplastic syndromes after other causes excluded.
- If associated with other paraneoplastic manifestations like cachexia, anorexia, fever.

Table 5: Magnetic resonance imaging finding in paraneoplastic neurological syndromes

There is no specific MRI finding for PNS. however the following findings may alert the clinician regarding PNS:

- Abnormal T2HI signal in medial temporal region suggestive of limbic encephalitis
- Abnormal T2 HI in mesial temporal lobes, hypothalamus, basal ganglia, thalamus and upper brainstem collicular region- diencephalic/upper brainstem dysfunction
- Symmetric, longitudinally extensive tract or gray matter–specific changes on spinal MRI[41]

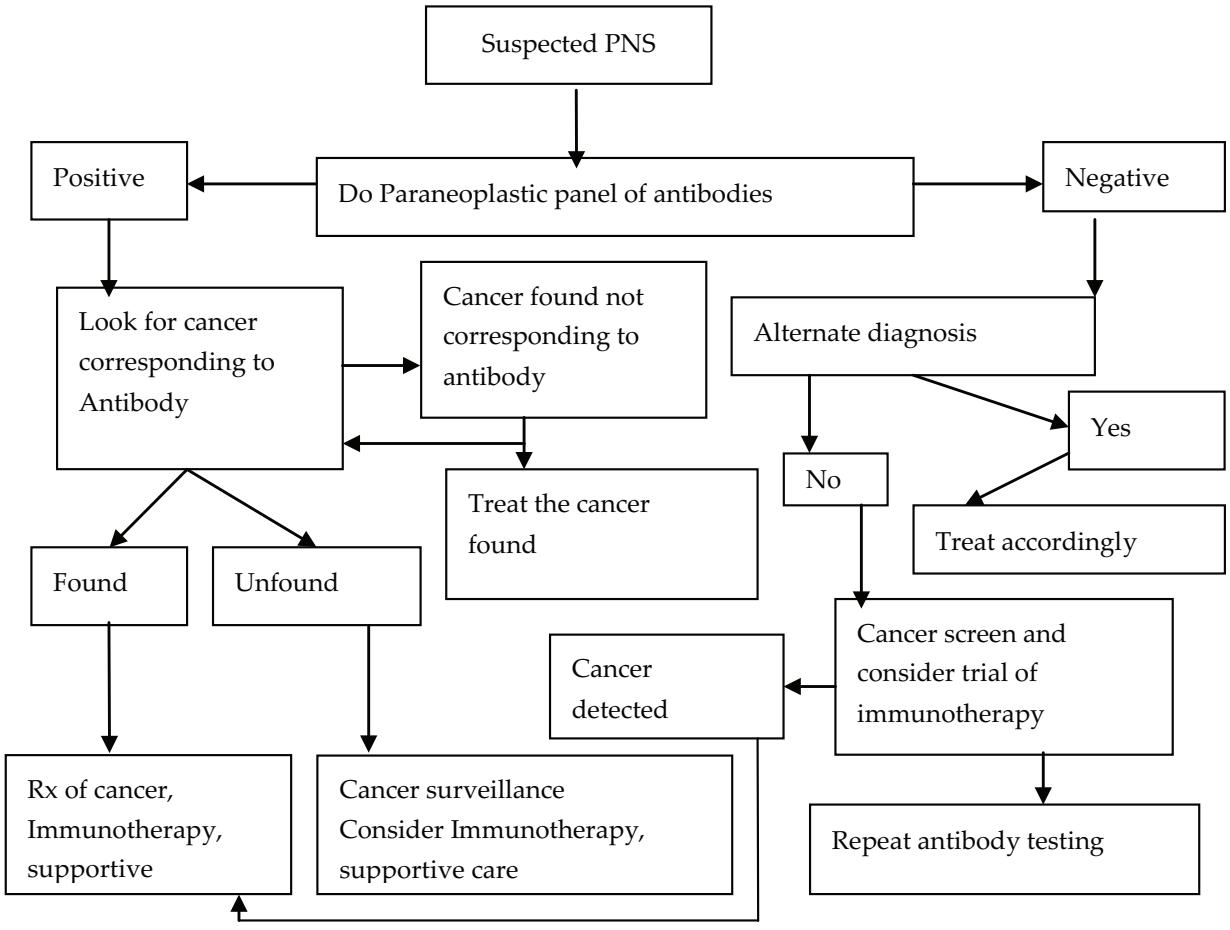

Figure 1: Algorithm for diagnosis and management of paraneoplastic neurological syndromes

for a significant period, perhaps up to 4 years.[11] In cerebellar degeneration with PCA-1 positivity and negative mammogram, exploratory laprotomy is recommended if ovarian and Mullerian neoplasm are not otherwise detected.[12] Testicular ultrasound is an important part of the evaluation in males less than 40 years with suspected PNS, even if anti-Ma antibody is negative.

Treatment

Treatment of PNS includes treatment of the tumor, immunotherapy and supportive therapy. The best way to stabilize PNS is to treat the cancer as soon as possible. This includes surgical removal of tumor, chemotherapy and/or radiotherapy. There are no evidence-based recommendations available regarding the immunosuppressive therapy.

Immunotherapy includes steroids, intravenous immune globulins (IV IgG), plasma exchange, cyclophosphamide, azathioprine and rituximab. Those PNS mediated by antibody are more reversible; for example, PNS mediated by VGKC complex antibodies, AChR antibodies and NMDA receptor antibodies. In disorders with intracellular target antigens and a strong cellular immune reaction, damage is more severe and often irreversible. The common approach used in the autoimmune neurology clinic of Mayo Clinic is high-dose intravenous methyl prednisolone therapy. One gram of methyl prednisolone is administered intravenously for 5 days followed by weekly therapy of the same dose for 6–12 weeks. If there is response to trial therapy, medications like mycophenalate mophetyl or azathioprine can be considered for long-term immunosuppression. On the other hand, if there is no response, plasma exchange should be the next line in antibody-mediated disease. Other options include immunosuppression with cyclophosphamide. Rituximab may be useful in antibody-mediated diseases. Patient may need long-term treatment. For an individual patient, duration of treatment is usually determined by clinical response.

In anti-NMDAR encephalitis, Dalmau[13] has proposed a combined treatment as first-line -intravenous methyl prednisolone with IVIgG or plasma exchange. If there is good response to this, chronic immunosuppression with azathioprine or mycophenalate is recommended for 1 year. If there is no response, rituximab or cyclophosphamide, or both combined, should be given. If there is no response for the combined therapy of rituximab and cyclophosphamide, an alternate immunosuppressive like oral or intravenous methotrexate should be considered.

Supportive therapy includes symptomatic treatment like analgesics, antiepileptics, psychiatric medications, dysautonomia medications, physiotherapy, occupational therapy and speech and swallowing therapy. Respiratory support and nutritional support are important. 3, 4 diaminopyridine is used for symptomatic treatment of LEMS. Anticholinesterase inhibitors are used in the treatment of myasthenia gravis. Diazepam is used in Stiff Person Syndrome. Clonazepam and sodium valproate are administered in opsoclonus myoclonus.

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