EDITORIAL

Paraneoplastic Neurological Syndromes: What the Physician Should Know

Satish V Khadilkar[1], Bhagyadhan A Patel[2], Madhu Bala[3]

"It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so"

Mark Twain

Introduction

Physicians deal with a wide variety of neurological conditions. Particularly in our country, where there is a great shortage of clinical neurologists, a large number of patients having neurological disorders are looked after by the physicians.[1] Common categories of diseases such as strokes, infections of the nervous system, epilepsies, headaches and movement disorders do not pose problems for the physicians. When it comes to uncommon conditions like the group we are discussing here, things get a little uncomfortable for most clinicians-physicians and neurologists alike! The spectre of rare but treatable conditions is always haunting the treating doctor. He knows that the common diseases are common and hence he will see large volume of these in his daily work, but the uncommon ones will fool him from time to time and he has to 'catch' these as well.

In this context, it is important to appreciate that para neoplastic neurological syndromes (PNS) exist and will make their appearance in consulting rooms of physicians once in a while. So, let us be conversant with these uncommon and intriguing neurological conditions that are potentially treatable. PNS are immune mediated manifestations of cancer and not direct results of the spread of cancer. Tumors express auto antigens that are shared with the nervous system and thus, result in antibody mediated damage to the central, peripheral or autonomic nervous system. In the recent years, our abilities to characterize such antibodies and as a result the yield of PNS have improved.[2]

Is this a paraneoplastic syndrome?

In post graduate clinics and ward rounds, this question often comes up. Following are the clinical guidelines which help the diagnosis.

PNS generally precede the diagnosis of malignancy by a few months. Uncommonly, these develop in a patient known to have a cancer. The intervals between their appearance and that of cancer can be very long, stretching in years in some cases.

The clinical evolution of PNS exhibits a rapid tempo, evolving over weeks to months. Exceptionally, they are slow, going over years and such patients tend to be confused with neurodegenerative or genetic conditions.

PNS follow patterns of clinical involvements, within the central, peripheral or the autonomic nervous systems. Table 1 summarizes the well-recognized PNS. Out of these, Lambert Eaton myasthenic syndrome, sensory ganglionopathies, adult dermatomyositis and opsoclonus myoclonus syndrome are such that they evoke strong possibilities of a cancer in the body. On the other hand, presentations with ataxias and neuropathies have a wide differential diagnosis which the clinician will have to consider. In this issue of the journal authors make the important point of the clinical pattern of presentation and the tempo of the symptoms to be indicators of PNS and give illustrative cases of the classical PNS.[3]

A proportion of PNS are clinically less evident and are listed in table

Table 1: Well characterized PNS and associated malignancies

Name of PNS	Malignancy	Antibodies (onconerual or neuronal cell surface)
Central Nervous System		
Limbic encephalitis	SCLC, Testicular germ cell tumors, ovarian teratoma, thymoma and hodgkin lymphoma.	Anti Hu, CV2/CRMP5, VGCC, Ma, Amphiphysin, AMPA, GABA, LGI1, GAD-65, mGluR5.
Encephelomyelitis	SCLC, Breast, thymoma	Anti Hu, CV2/CRMP5, Amphiphysin
Cerebellar syndrome	Breast, SCLC, Ovary and hodgkin lymphoma	Anti Hu, CV2/CRMP5, Ri, Yo, Tr, mGluR1, VGCC
Opsoclonus myoclonus syndrome	Neuroblastoma, SCLC, Breast and ovary	Anti Ri, Hu, Ma
Visual System		
Retinopathy	Melanoma, SCLC	Anti bipolar cell and anti-recoverin
Peripheral nervous system		
Sensory ganglionopathy	SCLC, various other solid tumors	Anti Hu, CV2/CRMP5, VGCC
Neuromuscular junction and Muscle		
Lambert Eaton myasthenic syndrome	SCLC, lymphoma	Anti VGCC, Anti Hu, Sox1
Dermatomyositis	SCLC, breast, ovarian, gastric cancer.	Anti Tifi y

SCLC, small-cell lung cancer; *VGCC*, voltage-gated calcium channels;;*NMDA*, *N*-methyl-D-aspartate receptor; *GABAB*, gamma-aminobutyric acid-B receptor; *AMPA*, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; VGKC,voltage-gated potassium channel,*LGI1*, leucine-rich glioma inactivated protein-1; *CASPR2*, contactin-associated protein-like 2; *GABA*, gamma-aminobutyric acid-A receptor; *mGluR5*, metabotropic glutamate receptor 5; *mGluR1*, metabotropic glutamate receptor 1.,GAD-65,glutamic acid decarboxylase

[1]Professor and Head, Department of Neurology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra; [2]Consultant Neurologist, Sterling Hospital, Ahmedabad, Gujarat; [3]Resident, Department of Neurology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra

Table 2: Other presentations of PNS

Name of PNS	Malignancy	Antibodies (onconerual or neuronal cell surface)
Central nervous system		
Brain stem encephalitis	SCLC,Testicular germ cell tumors	Anti Hu, Ma, Ri
Characterstic Encephalitis	Ovarian teratoma,Rarely SCLC,breast,Hodgkin lymphoma,Testicular germ cell tumor.	Anti NMDA
PERM (Progressive encephalomyelitis with rigidity and myoclonus)	Breast, SCLC and Hodgkin lymphoma	Anti amphiphysin, glycine receptor antibodies
Morvan syndrome	Thymoma	Anti-CASPR2 (VGKC)
Visual System		
Uveitis	SCLC	Anti CV2/CRMP5
Optic neuritis	SCLC	Anti CV2/CRMP5
Spinal cord		
Stiff person syndrome	Breast, SCLC and Hodgkin lymphoma	Anti amphiphysin, glycine receptor antibodies, GAD-65
Myelitis	SCLC, Breast	Anti Hu,Amphiphsin
Peripheral nervous system		
Sensorimotor neuropathy	SCLC, thymoma, breast, Multiple myeloma	Anti CV2/CRMP5
Mononeuritis multiplex	SCLC, Lymphoma, ca colon, kidney, bile duct, stomach and prostate	Anti Hu
CIDP with or without POEMS	Osteosclerotic myeloma	-
Neuromyotonia	Thymoma	Anti VGKC (CASPR2)
Neuromuscular junction and Muscle		
Myasthenia gravis	Thymoma	Anti AchR, titin
Acute necrotizing myopathy	Solid tumor eg. SCLC, Bladder, breast, Gastrointestinal tract	-

SCLC, small-cell lung cancer;*NMDA*, *N*-methyl-D-aspartate receptor; *POEMS*,*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, and *s*kin changes; *CASPR2*, contactin-associated protein-like 2; *AChR*, acetylcholine receptor

Table 3: Differences in PNS resulting from intracellular or cell surface antigens

	Intracellular antigens	Cell surface antigens
Pathogenesis	T cell mediated	B cell mediated
Antibody specificity	React with all neurons of neuroaxis	Specific receptors
Cerebrospial fluid inflammatory changes	Common	variable
Response to immunotherapy	Poor	Good
Cancer association	Always (Except GAD65)	Can occur with or without underlying cancer
Classical antibodies	Eg:anti Hu, Ri, Yo, CV2/CRMP5, Amphiphysin, Ma, sox1, GAD65	Eg:NMDA, VGKC(LGI1 and CASPR2), GABA-A, GABA-B, AMPA, mGluR5, mGluR1, Glycine, VGCC.

Table 4: Clinical clues to specific diagnosis

Clinical clues	Specific antibody	Tumor
Young woman, psychosis, dystonia and autonomic instability	NMDA	Ovarian tumor
Older man, faciobrachial dystonic seizures	VGKC (LG-1)	SCLC
Myokymia	VGKC (Caspr2)	Thymoma
Increased muscle tone, muscle spasms and hyperekplexia	Glycine receptor	Breast, SCLC
Sensory ataxia, gastroparesis and multiple regions of nervous system involved	Anti-Hu	SCLC
Daytime hypersomnolence and eye movement abnormalities	Anti-Ma	Testicular tumor

2. These have a wide differential diagnosis and are more likely to be missed as compared to the classical syndromes. It is indeed this area where the clinician should be alert to the possibility of PNS and investigate, wading through the wide differential diagnosis.

A combination of two classical paraneoplastic syndromes in one patient is uncommon. Such combinations raise various possibilities besides PNS. A variety of system degenerations (e.g. spinocerebellar ataxias) and mitochondriopathies, more often than not, exhibit combinations of dysfunctions of parts of the nervous system. Also, when the central as well as the peripheral nervous systems are affected in the same individual, the categories of toxic, deficiency, metabolic and degenerative disorders are more likely.

Some of the antibody associated classical syndromes can occur with or without cancer, this is specifically true for antibodies against neuronal cell membrane as mentioned in table 3, their response to treatment is better as compared to antibodies against neuronal intracellular antigens.[4,5]

The presence of risk factors for malignancy such as smoking or strong family history should prompt evaluation of underlying malignancy.

Some clinical clues can be useful for further workup and diagnosis of a suspected case of PNS as shown in Table 4.

How to prove PNS?

Once a paraneoplastic syndrome is clinically suspected, it is important to go over all the systems in the clinical history and examination if the patient is not already known to harbour a cancer. Appropriate antibody testing is the next step and Table 1 shows the antibody associations. In a proven case of cancer as well, we need to send the appropriate antibody studies to clarify the causal association. Presently, most laboratories offer panels of antibodies and while these are useful and cost effective, it is important to make sure that the antibodies of interest have been included. Patients with lung cancer tend to have higher proportion of incidental antibodies and thus, mere presence of antibodies is not enough to establish that a particular clinical presentation has a paraneoplastic cause. Hence, proper classification of clinical syndrome is of prime importance and antibody test results must be interpretated in this context. When serum antibodies are absent, testing antibody levels in CSF is preferred e.g. CSF NMDA level is gold standard as compared to serum assays. Table 5 mentions syndrome based evaluation.

When the clinical suspicion is strong and the cancer is not yet detected, in the present times, a whole body PET CT scan helps in the detection of the tumor. While PET CT scan can be used as a broad detection

Table 5: Some examples of syndrome specific tumour screening

Syndrome	Antibodies	Preferred imaging modalities
Young woman with limbic encephalitis	NMDA	MRI pelvis with contrast
Woman with cerebellar degeneration	Anti- Yo	Pelvic and breast MRI with contrast
Multiple regions of nervous system involved	Anti-Hu	Chest CT with contrast
Limbic encephalitis	DNER and mGLuR1	Chest, abdomen and pelvis CT with contrast for Hodgkin's lymphoma and lymph node biopsy
Young man with brainstem encephalitis	Ma2	Ultrasound of testis

measure, it is important to remember that all the tumors are not shown on this scan, for e.g, gonadal tumors, neuroblastoma, thymoma, prostatic carcinoma and mucosa predominant tumors can evade detection. Authors have had a patient with oesophageal carcinoma which hid from the PET CT; patient having presented with late age dermatomyositis. Another important point is that corticosteroid therapy can alter the antibody levels, which should be borne in mind.

How to keep a vigil when PNS is suspected and cancer not detected?

This situation calls for periodic clinical and investigative reviews. While there is no set pattern of follow-ups, one could begin with a three monthly clinical review of going over full history and clinical examination and performing clinically directed investigations. Repeating antibody levels may not serve much purpose as the severity of the syndrome does not consistently link with the antibody titers. How long to keep the follow up is a grey area and five years could be very broadly considered as adequate.

How to treat PNS?

PNS are not easy to treat and in the author's experience, only a minority of patients has improved substantially. However, as there is a potential of improvement, therapy trials should be offered. Treatment of the neoplasm, (removal, chemotherapy or radiotherapy) can bring about some relief to the symptoms of PNS. While this is logical, as the tumor is believed to participate in the antibody production; there can be a lack of improvement. As PNS are antibody mediated diseases, logically, immunotherapies have been employed. When devastating neuro deficits exist, for rescue, plasma exchange or intravenous immunoglobulins can be gainfully employed, albeit for short lasting relief. Corticosteroids are the mainstay of long term maintenance of functionality; does titrated to produce best benefit and least encumbrance. The role of steroid sparing agents is unclear and has to be tailored to the individual situation which takes in to account the benefit potential and the total perspective of life expectancy and quality.

What is the outlook?

When a neurological paraneoplastic syndrome gets identified, it helps the search and detection of the malignancy which as yet has not announced itself and in that way, the patient may get benefits of early diagnosis. Dealing with the primary tumour and immunotherapy are known to reduce the impact of the disability but spectacular recovery or normalcy is not common. Hence the patient and family need counselling and rehabilitative programs for coping up with the disability. Chemotherapeutic agents and radiotherapies can add to the limitations (e.g neuropathy) and need to be kept in mind, while discussing the total outlook.

References

1. Khadilkar SV. Neurology: scenario in India. *J Assoc Physicians of India* 2012; 60:42-44.
2. Leypoldt F, Wadinger KP. Paraneoplastic neurological syndromes. *Clinical and Experimental Immunology* 2014:175; 338-346.
3. Ojha P, Jagiasi K, Chheda A, Soni G, Peddawad D, Kadam N, Patil S. Does the Tempo and Pattern of Neurological Syndrome Help Diagnose Paraneoplastic Etiology? *J Assoc Physicians of India* 2018; 66:14-18.
4. Dalmau J, Myrna R Rosenfeld F. Paraneoplastic syndromes of the CNS. *Lancet Neurol* 2008; 7: 327–40.
5. Lancaster E. continuum (Minneap Minn) 2017; 23:1653-1679.