Does the Tempo and Pattern of Neurological Syndrome Help Diagnose Paraneoplastic Etiology?

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Abstract

Background: Paraneoplastic neurological syndromes (PNS) are defined as remote effects of cancer that are not caused by the tumor and its metastasis, or by infection, ischemia or metabolic disruptions. In most patients, the neurological disorder is the manifesting condition and cancer is not detectable clinically at that time. Therefore, most often it will be upon the neurologist and not the oncologist to detect paraneoplastic syndrome.

Aims and Objectives: To identify characteristic features of a neurological syndrome (presentation pattern and tempo of illness-onset, duration, progression and response to treatment) which indicate a paraneoplastic etiology.

Materials and Methods: This is a retrospective study. Medical records of all patients who were discharged/died in Neurology unit of a tertiary care center over a study period of two years with a diagnosis of Paraneoplastic neurological syndrome as per the diagnostic criteria given by F Graus et al¹ were studied.

Results: Seven PNS cases were identified of which, five had peripheral and two had central nervous system syndrome consistent with the anatomical localisation. Painful pure motor quadriparesis was present in three cases. Subacute onset and rapid progression were seen in six out of seven patients. Ill sustained response to corticosteroid treatment was seen in three patients whereas the remaining four showed no response. In five patients, tumour was detected after the diagnosis of neurological syndrome, as against one patient which had an antecedent tumour and the remaining one patient had classical onconeural antibody without evidence of any detectable tumor. Average time to tumor diagnosis from neurological symptom was 3.5 months.

Conclusion: A subacute onset, rapidly progressive painful, pure motor quadriparesis; Ganglionopathy in elderly and autoimmune encephalitis with ill sustained or no response to corticosteroids merits consideration of paraneoplastic etiology.

Introduction

Paraneoplastic neurological syndrome (PNS) is defined as remote effects of cancer that are not caused by the tumor and its metastasis, or by infection, ischemia or metabolic disruptions.² PNS is rare, affecting 1/10000 cancer patients.² PNS can present either as UMN or LMN syndrome, affecting different anatomical structures of the neurological system (brain parenchyma (Cerebellar degeneration, Encephalitis),³ In most patients, the neurological disorder is the manifesting condition and cancer is not detectable clinically at that time. Thus the neurologist has the charge of identifying a neurological disorder as paraneoplastic.² PNS are usually known to be severely disabling and so need prompt diagnosis to help early treatment of tumor.³ Many PNS are associated with antibodies (onconeural antibodies), suggesting the immune process. These antibodies are specific (more than 90%) but not sensitive, present in less than 50% patients with PNS. Thus absence of antibodies cannot rule out PNS.³ Considering the rarity of PNS and the aforementioned difficulties, diagnosing PNS is challenging. Limited data is available on the characteristics of PNS from our country. The study was thus undertaken to understand the tempo and pattern of various PNS to help suspect the diagnosis of PNS which in turn can help early diagnosis of clinically occult tumour. Early diagnosis and treatment of tumor can change the tumor prognosis.

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Material and Methods

This is a retrospective study. Medical records of all patients who were discharged/died in Neurology unit of a tertiary care center over a study period of two years with a diagnosis of Paraneoplastic neurological syndrome as per the diagnostic criteria given by F Graus et al¹ were studied. The hospital protocol is to first diagnose the patient into clinical anatomical localisation syndrome based on history and examination, followed by search for etiology. Search for malignancy is done in all suspicious cases. Diagnostic modalities like CT chest, CT abdomen, whole body PET CT, MRI Brain,
serum onconeural antibodies and tissue biopsy as indicated are used in suspected cases.

**Cases**

1. **LEMS**: 32 years female had 4 months duration painful progressive asymmetric quadriplegia, diplopia, ptosis, nasal speech, facial weakness and generalised areflexia. She improved transiently with corticosteroids but later developed autonomic dysfunction i.e. postural dizziness, excess sweating and diarrhoea. NCS showed low amplitude CMAPs with normal SNAPs. RNS showed decremental response, CMAP improved post 10sec exercise and rapid RNS showed more than 100% increment thus confirming presynaptic neurotransmitter defect (Figure 1a). She improved with pyridostigmine and was continued on corticosteroids. CECT chest suggested tumour in lower lobe of left lung, biopsy confirmed small cell lung cancer (Figure 1b). She was referred to oncology centre.

2. **Axonal polyradiculoneuropathy**: 60 years female presented with 6 months history of painful progressive symmetric pure motor quadriplegia with generalised areflexia without cranial nerve involvement. She had skin hyperpigmentation (Figure 2b) and pedal edema. EMG-NCS showed severe axonal polyradiculoneuropathy. CSF proteins were raised. She had kidney injury (serum creatinine 2.4 mg%), anemia (Hemoglobin 7.1 gm%) and proteinuria (890 mg/24 hours). She showed good response to steroids transiently but later started deteriorating despite steroid therapy. Further evaluation with X-ray profile and whole body PET CT revealed multiple lytic bone lesions (Figure 2a), Serum protein electrophoresis with immunofixation showed M band in IgG region. Urine BJ proteins were present and serum calcium was 10.3 mg%. Bone marrow biopsy confirmed Multiple Myeloma (Figure 2c). She fulfilled the diagnostic criteria for POEMS syndrome. Multiple Myeloma treatment with chemotherapy showed mild improvement in her paraneoplastic syndrome.

3. **Polymyositis**: 62 years female was admitted with subacute history (1 month) of painful pure motor progressive symmetrical quadriplegia (mainly proximal lower limbs) with depressed deep tendon reflexes. Raised CPK 1042 IU and EMG showing myopathic
potentials with fibrillations were suggestive of myositis, which was confirmed on biopsy (Figures 3a and 3b). Patient continued to worsen despite treatment with IV steroids and developed bulbar weakness requiring feeding tube.

CT chest and PET scan showed a thymoma, confirmed on open biopsy. She was referred to oncosurgery.

4. Ganglionopathy: 50 years female had subacute progressive incoordination with areflexia of upper limbs, then lower limbs and trunk over 1.5 months. NCS showed absent SNAPs in all four limbs with normal CMAPs suggestive of ganglionopathy. Vitamin B12 levels, ANA blot, lip biopsy and MRI cervical spine were all normal. No response to corticosteroid therapy made us suspect a paraneoplastic etiology. PET scan revealed carcinoma breast (Figure 4) which was treated surgically. She showed mild improvement in PNS on follow up.

5. Motor Neuron Disease: 75 years male, diagnosed case of Carcinoma bladder since 1 year presented with subacute history (2 months) of progressive pure motor quadriaparesis with wasting and fasciculations with exaggerated reflexes and bilateral extensor plantar responses. NCS EMG showed chronic denervation with reinnervation in cervical, lumbar and paraspinal muscles. Patient fulfilled El Escorial criteria for MND,5 patient showed rapid deterioration and succumbed.

Table 1: Paraneoplastic neurological syndrome and their characteristics

<table>
<thead>
<tr>
<th>Paraneoplastic syndrome</th>
<th>LEMS</th>
<th>Polymyositis</th>
<th>CIDP</th>
<th>MND</th>
<th>Ganglionopathy</th>
<th>Limbic encephalitis</th>
<th>Anti ma encephalitis</th>
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<tbody>
<tr>
<td>Associated Cancer</td>
<td>Small cell lung carcinoma</td>
<td>Thymoma</td>
<td>Multiple Myeloma</td>
<td>Carcinoma bladder</td>
<td>Carcinoma Breast</td>
<td>Thymoma</td>
<td>-</td>
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<td>75</td>
<td>70</td>
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<td>M</td>
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<tr>
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<td>Subacute</td>
<td>Chronic</td>
<td>Subacute</td>
<td>Rapid</td>
<td>Subacute</td>
<td>Rapid</td>
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<tr>
<td>Progression</td>
<td>Rapid</td>
<td>Rapid</td>
<td>-</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Rapid</td>
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<tr>
<td>Time to tumor diagnosis (months)</td>
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<td>7.5</td>
<td>-</td>
<td>2.5</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
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</tr>
</tbody>
</table>

Fig. 5a: MRI Brain FLAIR Images showing hyperintensities in bilateral temporal, insular, external capsule and corona radiata region

Fig. 5b: Complete resolution on repeat MR images after 6 weeks of steroids

Fig. 6: EEG is showing FIRDA in the left hemisphere
in 9 months from onset of neurological symptoms. In view of subacute presentation and rapid deterioration with background history of tumour, diagnosis of paraneoplastic MND was made.

6. Auto immune limbic encephalitis: 45 years female presented with subacute (2 months) history of forgetfulness, language difficulty and change in behaviour. MRI brain showed bihemispheric fluffy hyperintense lesions without any mass effect affecting bilateral medial temporal (Left more than right) and left frontal lobe (Figure 5a). CSF showed albumin-cytological dissociation, CSF NMDA and VGKC antibody were negative. She responded to immune therapy with corticosteroids and showed complete resolution of radiological lesions after 6 weeks (Figure 5b). Whole body PET CT showed anterior mediastinal hypermetabolic mass consistent with thymoma. Patient is advised thymectomy and is in remission on maintenance low dose steroids which is planned to be tapered and stopped after thymectomy.

7. Autoimmune Anti Ma Limbic encephalitis- 65 years female presented with subacute (3 months) rapidly deteriorating history of hyper-somnolescence, forgetfulness and behavioural changes. She had significant weight gain of 10 kg over last 3months. Her MRI showed bilateral medial temporal hyperintensity suggestive of limbic encephalitis and EEG showed FIRD consistent with encephalopathy (Figure 6). CSF examination was unremarkable. Anti Ma2 onconeural antibody was detected in serum. She did not have any evidence of tumour on whole body PET, CT chest and abdomen. She showed poor response to immune therapy (steroids and IVIG) and showed progressive deterioration in attention and orientation.

Paraneoplastic neurological syndrome cases have been summarised in Table 1 with regards to onset, progression and response to treatment.

Discussion

The study gives experience of Paraneoplastic Neurological syndrome from a tertiary care centre in India over a period of 2 years. Though PNS is rare, it can be severely disabling. Knowing the characteristics of PNS can help suspect them early and early diagnosis can improve tumour prognosis. There is not much literature on PNS from India except the case series from a centre in South India. Therefore this study is important as we bring out key features in our cases which help characterise PNS, increasing the awareness of these entity.

Challenges in the diagnosis of PNS

i. Diagnosis of Tumor: Tumor diagnosis often follows PNS diagnosis as the tumor is not apparent at presentation. In our study, only one patient was diagnosed with malignancy at presentation whereas in other patients, tumour was revealed after active search following suspicion of paraneoplastic etiology. In one patient, no tumor could be identified and patient had only presence of onconeural antibody.

ii. Sensitivity and specificity of Diagnostic tests: Onconeural antibody- Less than 50% patients with PNS have onconeural antibodies, however these are highly specific (>90%) for PNS.

iii. Delay in recognition of PNS:

a. Lack of facilities/ experts. Quite often the patients present to non-specialists. Rarity of this condition causes delay in diagnosis even at the hands of trained neurologists. In our study, five patients came from Interiors of state and had significant disability at the presentation.

b. Treatment response: Two of the five in whom steroids were started before admission showed improvement initially on treatment, but one deteriorated after 4 weeks of steroids and other worsened while steroid tapering was attempted after 6 weeks. Steroid response can delay the suspicion and diagnosis of PNS. As PNS is associated with antibodies against the neural antigens produced by the tumour, immune mechanism is suggested in some PNS and so the response to steroids or other immunotherapies can occur. c. Lack of awareness. Tempo and pattern of clinical syndrome is varied, PNS can affect any part of the neuro axis. Characteristics of PNS are described below to improve awareness and increase PNS recognition.

LEMS is due to presynaptic neuro transmission defect, it can be paraneoplastic and is present in 1% of small cell lung cancer. It is characterised by triad of proximal painful pure motor weakness, areflexia and autonomic dysfunction. Electrophysiologically, it is triad of low amplitude CMAPs, decremental response on slow RNS and incremental response on fast RNS. Ocular and bulbar features are seen in 30% and autonomic dysfunction in 60% within 3 months of onset. Hyporeflexia/ areflexia is usually universal (90-100%), however post exercise facilitation of reflexes can be observed in only 40% of patients with LEMS. Our patient had ocular, bulbar and autonomic involvement within 4 months of onset. She had areflexia but did not show post exercise facilitation. LEMS usually responds to pyridostigmine and immune therapy, however long-term clinical and pharmacological remission has been reported in patients following successful tumour resection.

Paraneoplastic polyneuropathies: It can be confused with chronic inflammatory demyelinating polyneuropathy (CIDP) and in lymphomas with direct infiltration of nerves (neurolymphomatosis). Sensorimotor polyneuropathies may antedate the diagnosis of multiple myeloma and sclerotic myeloma, which are typically associated with IgG or IgA paraproteins. Recent neurophysiological studies indicate that the polyneuropathy of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes) can be differentiated from CIDP by the presence of diffuse demyelination and more severe axonal loss as was seen in our case. Lenalidomide and dexamethasone are effective to control the neuropathy of POEMS patients who are not suitable for or progress after autologous stem cell transplantation.
Sensory Ganglionopathy may present with symptoms that do not raise the suspicion of a paraneoplastic origin. A recent study on sensory ganglionopathies of different causes identified paraneoplastic cases in a group of older (>60 years) male patients with subacute onset early pain, and frequent involvement of the arms.  

A rapidly progressive autoimmune disorder commonly associated with small cell cancers due to relentless destruction of dorsal root ganglion cells by cytotoxic T cells. Because neuronal damage is irreversible, early recognition may be the only means to prevent severe neurologic disability.  

An association between polymyositis and various cancers has been reported in the literature but it is still debated, as the published data lacks either lung cancer histologic differentiation or biopsy-based delineation between polymyositis and dermatomyositis.  

Polymyositis should be considered as a potential presentation of paraneoplastic syndrome, especially in patients who are at risk for lung cancer. The clinical course of myopathy is closely linked with the course of cancer.  

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Subacute onset, fairly rapid progression and/or tumor treatment.

2. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndrome (PNS) characterized by isolated or combined limbic, diencephalic, or brainstem dysfunction.  

Anti-Ma2 encephalitis is exceptional among other PNS associated with classical antibodies in that the response rate to treatment is relatively high. Severe neurological deficits or death can occur in a substantial proportion of patient, approximately one-third show neurological improvement and another 20 - 40% stabilise with immunotherapy and/or tumor treatment.  

Anti-Ma2 encephalitis is almost always associated with testicular germ cell tumors in men younger than 50 years and these patients show neurological improvement once the testicular tumor is treated.  

Conclusions

Suspicion of paraneoplastic etiology was raised in all cases on the basis of behaviour of the neurological syndrome, i.e tempo and pattern of presentation. Subacute onset, fairly rapid progression and poor response to standard therapy may point towards the possibility of PNS. Early recognition of PNS often helps in early tumour identification thereby improving the chances of survival and outcome.  

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References
