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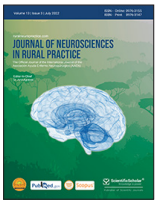

Brief Report

Initial experience in assessing diagnostic utility of conventional and functional imaging (staging CT, PET CT, and MRI Brain/Spine) in suspected cases of paraneoplastic neurological syndrome

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ABSTRACT

Objectives: Radiology receives a large volume of referrals for systemic scans and neuroimaging in suspected cases of paraneoplastic neurological syndrome (PNS) patients. To date, there have been no guidelines to define imaging pathways in diagnosis or surveillance of such patients. This article aims to evaluate diagnostic utility of imaging in detecting positive results as well as ruling out significant pathologies in suspected cases of PNS and strategize vetting requests.

Materials and Methods: Retrospectively evaluated scan records, onconeuronal antibody results of 80 patients (separated into below and over 60s age group) referred with suspected PNS (categorized as classical or probable PNS after neurological assessment). Imaging findings and final diagnoses were classified into three groups: Normal (N), non-neoplastic significant findings (S), and malignancies (M) after evaluating histopathology results/perioperative findings and treatment notes.

Results: There were ten cases of biopsy-proven malignancies and 18 cases of non-neoplastic significant conditions (predominantly neurological) with malignancies dominating in the elderly age group, demyelinating neurological conditions in below 60s group and patients suspected of classical PNS on neurological evaluation. Staging computed tomography (CT) had 50%, positron emission tomography CT (PETCT) had 80%, sensitivity had 93%, and negative predictive value in ruling out malignancy had 96%. Magnetic resonance of brain and spine was reported abnormal in 68% of finally diagnosed positive cases while only 11% cases demonstrated onconeuronal antibody positivity.

Conclusion: Complete neuroimaging before systemic scans, categorization of referral requests in probable and classical cases of PNS with prioritization of PET in cases of high clinical concern might help in better detection of pathologies and reduce unnecessary CTs.

Keywords: Paraneoplastic, Neuroimaging, Systemic scans, Malignancy, Onconeuronal antibodies

INTRODUCTION

Paraneoplastic neurological syndromes (PNS) constitute a heterogeneous group of neurological disorders involving both central and peripheral nervous systems. These precede the diagnosis of an occult malignancy. Radiology receives high volume of imaging requests including staging computed tomography (CTs), positron emission tomography (PET), and magnetic resonance imaging (MRI) scans to exclude cancers in such patients.

Mixed group of neurological presentations have been postulated to result from remote manifestations of certain tumor secreting peptides or from immune cross-reactivity between malignant and host nerve cells.[1,2] Management of PNS involves treatment of underlying tumors; hence, patients are subjected to a wide array of investigations. There are no standardized guidelines to define diagnostic pathway, next order of higher investigation, or frequency of surveillance scans. Overall incidence of PNS comprises < 1% of all cancer patients, but PNS might precede detection of cancer in up to 80% of cases; hence, search for an occult tumor is crucial.[2]

Objective

The purpose of this study was to assess diagnostic utility of imaging in suspected cases of PNS in detecting malignancy or alternative significant diagnosis and attempts to create an algorithm, which continues to be a grey zone.

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MATERIALS AND METHODS

We have retrospectively evaluated records of patients referred for imaging with suspected PNS in the past 2 years with approval of the Local Ethics Committee.

Inclusion criteria

A total of 80 patients who had staging CTs and complete neuroimaging by MRI brain and spine and had follow-up investigation records in our PACS and patient information system were included in the study. Initial staging CT/PET and MRI were considered as baseline scans. Thirty-one patients had PET CT oncology scans from base of skull to mid-thigh. Data set of our patients was divided in to two age groups, 60 years and above and below.

To remove subjective bias, we included cases in our study sample where two consultant radiologists, blinded to operative outcomes/histopathological results, independently assessed the baseline scans at presentation, and reached a consensus (100% interobserver agreement/kappa coefficient of (1) on imaging findings.

Exclusion criteria

Established cancer patients who presented with PNS in the course of their disease or treatment were excluded from the study. Our study population comprised only suspected PNS cases with no proven malignancy. No pediatric patients were included in the study.

Records of imaging studies, onconeuronal antibody in cerebrospinal fluid (CSF) and serum, follow-up scans, and histopathology results were evaluated. Results from imaging and antibody screening were compared with final diagnoses (FD) obtained from biopsy/treatment/perioperative findings.

Scans and medical records were evaluated 1 year from initial presentation.

Clinical criteria

Based on initial neurological assessment findings (obtained from patient records/clinical notes at the time of referral), clinical symptom complexes in our patients were categorized as *Classical* and *Probable* PNS by neurology colleagues as per PNS Euronetwork taskforce (EFNS) criteria.[3] Radiologists were not involved in categorizing these symptom complexes.

Assigned terms for imaging outcomes

Imaging interpretation from baseline scans was categorized into three groups: normal or benign findings (N), significant findings (S) which included systemic inflammatory/granulomatous/vasculitis such as conditions or suspicious actionable findings and third group consisting of obvious malignancies (M). Two radiologists with absolute agreement on scan findings coded imaging outcomes in these three categories based on initial baseline scan.

CT/PET criteria

Any obvious mass lesion and significant sized morphologically malignant appearing lymph nodes were considered as "M" on imaging.

Concerning or actionable findings on CT like mural thickening of a bowel wall, tumefactive focal consolidation in lungs which warranted further investigations were considered as "S."

Similarly, indeterminate non-physiological uptake on PET or actionable findings was considered as "S." Minor focal uptakes above the reference standardized uptake value in bowel, reactive nodes, and fibroid with no actionable concern mentioned in the reports and explained by benign etiologies were considered as "N."

MRI criteria

Apart from obvious mass lesions, unexplained abnormal signal pattern on MRI brain/cord reported as demyelinating lesions or inflammation of the CNS which progressed/persisted on follow-up scans, abnormal enhancement of brain parenchyma/nerve roots with actionable concern was considered as "S".

Insignificant age-related white matter signal changes with no progression, mild generalized atrophic changes, and incidental findings such as small meningiomas were considered as "N."

Summation of malignancy and significant diagnoses has been referred as total positive results from an individual test in following segments.

Scans were acquired in 64 slice MDCT scanner, 128 slice PET CT scanner, and 1.5 tesla MR machine.

FD, obtained from histopathology results, operative and follow-up scan findings, MDT outcomes, and treatment notes were similarly classified into N, S, and M. FD were coded after reviewing with neurological team and clinical colleagues.

Demyelinating conditions and diagnoses such as encephalopathy were coded as S, after going through patients' treatment notes, pathological tests, CSF analysis, immunological screening, and protein electrophoresis.

Cases of inherited myopathy or neuropathy were established on muscle or dural nerve biopsy with no biopsy amenable lesions or unremarkable baseline scans.

Patients with no M or S diagnoses established within 1-year period from the initial presentation were considered as negative and coded as N.

Diagnostic yield of individual imaging modalities in terms of sensitivity, specificity, positive, and negative predictive value was estimated and compared by subgrouping entire patient population into two age groups.

Finally, Pearson's Chi-squared was applied using SSPS version 25 to estimate any statistically significant difference in the distribution of pathologies between two age groups, between positive/negative antibody results, imaging findings, and FD. $P < 0.05$ was considered significant.

RESULTS

All 80 patients had CT and MR scans, 31 underwent PET scans (16 and 15 in under and over 60s groups, respectively). A complete record of CSF and serum antineuronal antibody screening records was available in 70 of our 80 patients with overall positivity in 7 cases (10%). Forty-five of our patients were below 60 years of age and 35 were 60 years and above.

Distribution of age-wise malignancy, significant and normal diagnoses made by each imaging modality and FD enumerated as shown in [Tables 1 and 2].

Thirty-two patients had classical presentations of PNS, while remaining 48 patients were categorized as probable PNS based on neurological assessment, relating to EFNS criteria.

CT sensitivity was less (50%) compared to PET (80%) in detecting malignancy although PET was done in a smaller sample of 31 patients. All five CT reports with malignancy diagnoses were confirmed as cancer on biopsy or follow-up; hence, CT specificity was 100% in our study sample [Table 3].

MR of the brain and spine was abnormal in 68% of final positive diagnoses; however, MRI sensitivity in detecting only malignancy was only 30% [Tables 3 and 4]. There were two CNS malignancies with one case of temporal glioblastoma and one case of CNS large B cell lymphoma with no systemic metastases on staging CT or PET. However, a case of small cell cancer with enlarged nodes in mediastinum and diffuse paraneoplastic thickening of the meninges and case of thymic carcinoma with nodular enhancement along cauda spinal nerve roots were observed as significant findings [Figures 1, 2a and b].

Antibody screening had an overall sensitivity of 11% in detecting positive diagnoses with high specificity close to 90% as most patients tested negative [Table 4].

Table 1: Distribution of malignancy, significant, and normal diagnoses made from each imaging modality and on final diagnoses.

Age Groups	Ab (*n*=70)		CT (*n*=80)			PET (*n*=31)			MRI (*n*=80)			Final Diagnosis (*n*=80)		
	Positive	Negative	M	S	N	M	S	N	M	S	N	M	S	N
<60	4	35	1	2	42	2	1	13	1	11	33	2	12	31
>60	3	28	4	4	27	4	4	7	3	7	25	8	6	21

Table 2: Malignant and other significant diagnoses finally established in two age groups.

	Malignancies	Other significant conditions
Under 60 years	(*n*=2) Thymic carcinoma Glioblastoma	(*n*=12) 1 Wernicke's encephalopathy, two demyelinating conditions in the central nervous system including idiopathic encephalomyelitis and multiple sclerosis, one peripheral axonopathy, one myelitis and one myelopathy, one subacute combined degeneration of the cord, two cases of myopathies, one phakomatoses (tuberous sclerosis), and two limbic encephalitis
Over 60 years	(*n*=8) 2 small cell cancers (mediastinal and colonic origin) one colonic adenocarcinoma one endometrial adenocarcinoma one follicular lymphoma in sublingual salivary gland tumor one CNS primary B cell lymphoma two poorly differentiated squamous cell cancer sampled from lymph nodes	(*n*=6) ADEM Creutzfeldt-Jakob disease Inflammatory myopathy Necrotizing inflammation of skull base. Vasculitis Chemical meningitis from ruptured dermoid

Table 3: Sensitivity and specificity of CT, PET, and MRI in detecting malignancy and non-malignancy findings.

CT (n=80)	Final Diagnosis		PET (*n*=31)	Final Diagnosis		MRI (*n*=80)	Final Diagnosis	
	Malignancy	Non- Malignancy		Malignancy	Non- Malignancy		Malignancy	Non- Malignancy
Malignancy	5	0	Malignancy	4	1	Malignancy	3	1
Non-Malignancy	5	70	Non-Malignancy	1	25	Non-Malignancy	7	69
Sensitivity = 5/5+5–50%			Sensitivity = 4/4+1–80%			Sensitivity = 3/3+7 (30%)		
Specificity = 70/0+70–100%			Specificity = 25/1+25–96.2%			Specificity = 69/1+69 (98.6%)		
PPV = 5/5+0–100%			PPV = 4/4+1–80%			PPV = 3/3+1 (75%)		
NPV = 70/70+5–93.3%			NPV = 25/25+1–96.2%			NPV = 69/69+7 (90.8%)		

CT: Computed tomography, PET: Positron emission tomography, MRI: Magnetic resonance imaging

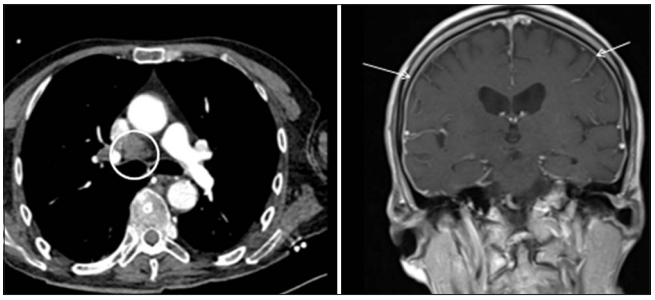

Figure 1: Axial contrast-enhanced computed tomography demonstrates enlarged mediastinal nodes. Coronal-enhanced MR brain shows diffuse pachymeningeal thickening (white arrows).

PET had a higher negative predictive value (NPV 96%) in ruling out a diagnosis of malignancy compared to CT (93%) and MRI (90%) [Table 3]. Overall NPV of MRI and onconeuronal antibody screening in ruling out positive diagnoses was high (84% and 93%) [Table 4]. Majority of positive cases with abnormal findings on MRI (18 out 28) had non-malignant neurological conditions.

A statistically significant difference was observed in the distribution of malignancy between two age groups p (0.013) with the higher number in above 60s age group. However, no significant difference was found in the distribution of malignancy between male and female patients ($P = 0.933$).

There was statistically significant difference in distribution of positive and negative diagnoses in between patients with classical and probable PNS on neurological assessment ($P = 0.002$) [Table 5] with the higher number of positive diagnoses among patients with classical PNS.

Similarly, statistically significant difference seen in the distribution of positive and negative diagnoses made from staging CT ($P = 0.003$) or antibody screening ($P = 0.00$) compared to the final established diagnoses [Table 5].

DISCUSSION

We noticed a statistically significant difference in distribution of pathologies between age groups with malignancies far less in younger population. Patients with classical symptoms of PNS had higher rate of positive diagnoses in the final outcome. PET had a better sensitivity in detecting malignancies and ruling out cancers whereas only staging CT/antibody screening was not adequate to detect significant pathologies. Neuroimaging detected abnormal signal in significant proportion of pathologies, particularly in younger population with predominance of non-malignant demyelinating pathologies. Overall NPV of all three imaging modalities in ruling out significant and malignant conditions was superior compared to sensitivity of tests in reaching positive diagnosis. Apparent high specificity and negative

Table 4: Sensitivity and specificity of MRI and antibody in detecting positive diagnoses (Malignancy and Significant conditions) against normal findings.

MRI (*n*=80)	Final diagnosis		Antibody Screening (*n*=70)	Final diagnosis	
	Positive	Normal		Positive	Normal
Positive	19	3	Positive	3	4
Normal	9	49	Normal	24	39
	Sensitivity=19/19+9 (67.8%) Specificity=49/3+49 (94.2%) PPV=19/19+3 (86.4%) NPV=49/49+9 (84.5%)			Sensitivity=3/3+24 (11.1%) Specificity=39/4+39 (90.7%) PPV=3/3+4 (42.9%) NPV=39/39+3 (92.9%)	

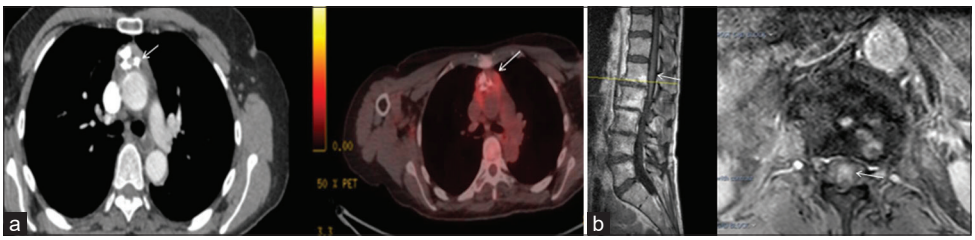

Figure 2: (a) Axial computed tomography and FDG PET scan demonstrates calcified mass with moderate uptake of FDG in anterior mediastinum, biopsied, and confirmed as thymic carcinoma. (b) Sagittal and axial gadolinium-enhanced T1 Fat saturate (T1FS) MR images demonstrate conus and cauda equine nerve root enhancement (white arrows) in the same case.

predictive values observed in all modalities explained by the fact that ultimately percentage of malignancy cases was significantly low compared to a large majority of negative cases.

Classical PNS conditions have been more commonly associated with particular subset of malignancies, although none of these conditions is uniquely paraneoplastic and can be associated with infective, inflammatory, metabolic, or idiopathic conditions.[3,4] In our study, majority of the established neurological demyelinating conditions had no primary malignancies detected on staging scans and within 1 year of follow-up.

The previous studies documented increased incidence over 60 years, with the highest incidence rate reported in 70–74 years age group and median age of 68 years. Based on this, we decided to take 60 years as cutoff, for dividing age groups.[5,6]

Key take away points from our observations:

1. Higher proportion of positive diagnoses among patients referred with classical PNS symptoms; hence, classifying symptoms as "classical" versus "probable" might help to categorize high priority referrals.
2. About 10% positivity for onconeural antibodies in our cases although, the previous studies documented 20–60% positivity and absence of well-characterized antibodies in up to 50% PNS.[7,8] Hence, onconeuronal antibody was not considered as a major determinant in considering or excluding systemic scan.
3. Majority of suspected PNS presentations below 60 years population were explained by primary neurological conditions in FD; hence, initial MRI of brain and spine and neurological check-up should be considered before systemic scans.
4. PET might be prioritized, in cases with strong clinical concern for occult malignancy, classical PNS, and well-characterized onconeuronal antibody association. The previous studies scored higher efficacy of PET over CT in detecting cancer, with increased role of contrast-enhanced PET in small head-and-neck and GIT malignancies.[1,9] Current practice of PET CT after a negative staging CT adds to increased radiation dosage and work burden for radiology.

Our retrospective and non-randomized study with small sample size and limited period of follow-up in a heterogeneous population is restricted in evaluating accuracy or cumulative benefits of repeat scans but provides a template for larger studies in the future. A 5-year follow-up with 6 monthly clinical and radiological surveillance has been advised in the previous literatures.[2,7]

Table 5: Weighted Chi-squared test in distribution of positive and negative established diagnoses between patients with classical and probable presentation of PNS and from CT and antibody results.

		Presentation symptoms			CT results			Tests		
		Classical PNS	Probable PNS	Total		Final Diagnosis	CT	Total	Final Diagnosis	Antibodies	Total
Findings	Positive	17	9	26	Findings	Positive	28	11	39	Positive	27	7	34
	Normal	15	39	54		Normal	52	69	121	Normal	43	63	106
Total		32	48	80	Total		80	80	160	Total	70	70	140
Pearson Chi-square-*P* value (0.002)					Pearson Chi-square-*P* value (0.003)				Pearson Chi-square-*P* value (0.000)				

CONCLUSION

PNS is a heterogeneous group with wide-ranging etiology apart from malignancies, especially in relatively younger (below 60 years) population. Thorough neurological check-up and neuroimaging and categorization of referral requests in probable and classical cases of suspected PNS before systemic scans with option for prioritization of PET in cases of high clinical concern might help in systematic vetting of such imaging requests and reduce burden of unnecessary scans.

Declaration of patient consent

Patients' consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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