Original Article

Clinical Spectrum, Therapeutic Outcomes and Prognostic predictors in Paraneoplastic Neurological Syndromes – Experiences from a Tertiary Care Center in India

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Abstract

Background: Paraneoplastic Neurological Syndromes (PNSs) are a heterogeneous group of immune-mediated disorders that often precede tumor diagnosis. There are few systematic studies on the spectrum and follow-up of PNSs. **Objective:** To analyze the clinical spectrum, associated tumors, antibody profile, outcomes, and prognostic predictors in a cohort of PNSs admitted in a tertiary care center. **Methods:** This retrospective study included 97 patients (2008-2019). PNSs were further classified as "classical," "nonclassical," "definite," and "possible." Clinical profile, diagnostic strategies, therapeutic options, and predictors of outcomes were identified. **Results:** The median age was 54 years (range 17–81). Thirty-nine (40.2%) had classical PNS, and 58 (59.8%) had nonclassical PNS, 74 (76.3%) had "Definite" PNS while 23 (23.7%) had "Possible" PNS. Cerebellar degeneration, peripheral neuropathy, and encephalopathy were the three most common neurological syndromes. Tumors were diagnosed in 66 (68%) patients; Lung cancer was the most common primary tumor. Antibodies were positive in 52 (53.6%). Anti-Yo antibody and anti-Ma2 antibody were the most common antibodies. The majority (57.7%) received immunotherapy in addition to definitive treatment for the tumor. A good outcome was seen in 53 (54.6%). Factors associated with good outcome were: early diagnosis, mRS <3 at presentation, absence of metastatic disease, and adjuvant immunotherapy. **Conclusion:** A high index of clinical suspicion is essential for early diagnosis and prompt management of PNS, especially the nonclassical syndromes. Multimodality diagnostic imaging techniques and antibody profiling play a crucial role in the diagnosis. A favorable prognosis can be expected with the judicious use of immunotherapy and definitive treatment of malignancy.

Keywords: Classical and nonclassical syndromes, modified Rankin Score, onconeural antibodies, Paraneoplastic Neurological syndromes

Introduction

Paraneoplastic Neurological Syndromes (PNSs) are a heterogeneous group of disorders associated with cancer but are not related to tumor infiltration, metastasis, or treatment-related side effects. They can present with central, peripheral, or autonomic nervous system involvement.[1] While precise estimates are unavailable, approximately 0.5-1% of all patients living with cancer have clinically disabling PNS.[2] The expression of various neuronal proteins by tumor cells triggers immune responses that are misdirected against the nervous system and result in neurological deficits. Autoimmunity, either humoral or cell-cytotoxicity mediated, is often the basis of pathogenesis. Paraneoplastic autoimmunity has a unique pathogenesis that is different from the classical autoimmune diseases. It is more severe and often presents with a broader range of clinical signs and symptoms.[3]

PNS is often underdiagnosed due to its complex nature, presentation before the malignancy becomes clinically overt, and the absence of specific imaging and laboratory abnormalities. Most of the literature on PNSs are from European or American centers and predominantly caucasian population.

Despite India's vast population and increasing cancer rates, there are no large studies on PNSs from India. This extensive cohort analyses various PNSs, their clinical profiles, association with different types of tumors and antibodies, diagnostic strategies, therapeutic options, and predictors of outcome at a large single-center in South India.

Methods

We present a retrospective study of consecutive patients (aged more than 16 years) diagnosed with PNS between

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January 2008 and January 2019 at a tertiary care teaching hospital in South India. The study was approved by the Institutional Review Board and Ethics Committee.

Data extracted from our prospectively maintained electronic database included clinical and demographic profiles, relevant investigations, details of associated tumors, onconeural antibodies, treatment received, functional status using modified Rankin Scale (mRS), and outcome. Cancer screening modalities included tumor-markers, chest radiographs, Ultrasound abdomen, Computerized Tomogram (CT), Mammogram, and Positron Emission Tomogram (PET-CT). Brain and spinal cord Magnetic Resonance Imaging (MRI), Nerve Conduction Studies (NCS), Electroencephalogram (EEG), and Cerebro-Spinal Fluid analysis were done as indicated. We excluded metastasis, causing neurological involvement before labeling as PNS.

Syndrome and antibody classification

We identified the PNS as "classical" or "nonclassical," and "definite" or "possible" based on combining a set of criteria proposed by Graus *et al*.[4] The term "classical syndrome" applies to those neurological syndromes that are often associated with cancer and have a typical clinical presentation. The "nonclassical" syndromes are sometimes associated with cancer but more frequently develop in their absence. The associated antibodies were grouped into well-characterised, and partially characterised onconeural antibodies based on their proven association with PNS reported in literature. The testing of onconeural antibodies was done by immunoblot using EuroimmuneIgG, Lubeck, Germany. Anti-Hu, Yo, CV2, Ri, Ma2, amphiphysin, and SOX1 were the well-characterised antibodies in the cohort. The partially characterised antibodies included anti-Tr, Recoverin, Zic4, Titin, and GAD65. The cell surface antibodies like N-methyl-D-aspartate (NMDA)-receptor antibody,[5] leucine-rich glioma-inactivated-1 (LgI1),[6] and contactin-associated protein-like2 (CASPR2) antibodies[7,8] have a weaker tumor association[9] and were included in the study only when they were associated with a tumor. The anti-NMDARantibody in serum and CSF was examined by immunofluorescence test.

Subjects identified were screened using an adaptation of the criteria proposed by Graus *et al*.[4] [Table 1].

Treatment and outcomes

The functional status was assessed comparing the mRS during admission, at the end of six months and the last follow-up. A "good outcome" was defined as improvement in the mRS score by at least one at the end of 6 months. Patients received treatment of the primary tumor, immunotherapy, symptomatic therapy, or a combination of these. The treatment of the primary included surgical removal, chemotherapy, radiotherapy depending on the cancer. The choice of immunotherapy was based on the discretion of treating neurologist. The treatment modalities included pulse dose steroids, intravenous immunoglobulin, and plasmapheresis. Second-line agents included cyclophosphamide and rituximab.

Statistical analysis

For statistical analysis, we used proportion as a descriptive statistic for categorical and ordinal variables, median and interquartile range for ordinal and continuous variables, and mean (SD) for continuous variables. Categorical variables were analyzed using the Chi-square test. Univariate and multivariate logistic regression models were used to determine the relationship of different variables with the outcomes. Survival curves were computed using the Kaplan-Meier method. Analyses were performed using statistical software IBM SPSS Version 22.

Table 1: Inclusion and Exclusion criteria

Inclusion Criteria (adapted from Graus *et al*.,[4] 2004)
1) Criteria for Definite Paraneoplastic Neurological Syndrome
a. A neurological syndrome (classical or not) with well-characterized onconeural antibodies (anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin) and no cancer
b. A non-classical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy provided that the syndrome is not susceptible to spontaneous remission
c. A non-classical syndrome with onconeural antibodies (well-characterized or not) and cancer that develops within five years of the diagnosis of the neurological disorder
2) Criteria for Possible Paraneoplastic Neurological Syndrome
a. A neurological syndrome (classical or not) with partially characterized onconeural antibodies and no cancer
b. A non-classical syndrome, no onconeural antibodies, and cancer present within two years of diagnosis
Exclusion Criteria
a. Age< 15 years
b. Patients with paraproteinemic neuropathy and thymomatous myasthenia gravis*
c. Cell surface antibodies (NMDAR, LG1, CASPR2) associated syndromes without tumors
d. Classic syndrome, no onconeural antibodies, no cancer but a high risk of an underlying tumor (one of the criteria for definite PNS in original Graus *et al*. criteria)

* Two exceptional cases of myasthenia were included because of their association with other tumors

Results

Clinical-demographic profile

A total of 97 patients diagnosed with PNS were included. There were 58 males and 39 females in the study, and the median age was 54 years (range 17–81 years). Seventy-four (76.3%) patients had "Definite"PNS, while 23 (23.7%) had "Possible"PNS. The distribution of various PNS is given in Table 2.

While central nervous system (CNS) involvement was seen in 51.4%, peripheral nervous system involvement and autonomic nervous system involvement were seen in 47.6% and 1% of patients. Multifocal patterns with more than a single PNS was found in 12.3% of patients. PCD was often associated with other syndromes such as LEMS syndrome (8.6%), peripheral neuropathy (8.6%), and opsoclonus-myoclonus syndrome (4.3%).

Table 2: Paraneoplastic Neurological Syndromes (PNSs)

Type of PNS	Patient No (%) (n = 97)*
Classic syndromes	**39 (40.2%)**
Paraneoplastic Cerebellar degeneration (PCD)	23 (23.7%)
Limbic encephalitis	5 (5.1%)
Sensory neuronopathy	5 (5.1%)
Lambert Eaton Myasthenic Syndrome (LEMS)	4 (4.1%)
Encephalomyelitis	2 (2.1%)
Dermatomyositis	2 (2.1%)
Nonclassic syndromes	**58 (59.8%)**
Sensory-motor neuropathy	16 (16.5%)
Motor neuron disease	10 (10.3%)
Multifocal encephalitis	9 (9.3%)
Autoimmune encephalitis	5 (5.1%)
Atypical Parkinsonism	6 (6.2%)
Neuromyotonia	5 (5.1%)
Myasthenic syndrome	2 (2.1%)
Optic neuritis	2 (2.1%)
Others (Polymyositis, Chorea, Dysautonomia)	7 (12.1%)

Paraneoplastic Neurological Syndrome (PNSs)*the data do not sum to 97 because some patients had more than one PNS

The majority of patients had a sub-acute presentation (50.5%), while the remaining had chronic (32%) or acute (17.5%) presentation. The mean duration of symptoms to diagnosis was 9.4 months (SD-12.77) for classic syndromes, 12.4 months (SD-14.02) for nonclassic syndromes, 10.8 months (SD-11.13) in cases of PNS without malignancies and 6.1 months (SD-8.10) in known cases of malignancies (P 0.03).

The comparison of various subgroups of patients based on the type of syndrome, the presence of tumors and, antibodies are listed in Table 3. The various tumors and antibodies associated with common PNSs are listed in Table 4.

Tumor profile

Tumors were detected in 66 (68%) patients. Lung cancer was the most common primary tumor 13 (19.6%), followed by ovarian tumors in 12 (18.2%). The most common type of cancer was small cell carcinoma lung. The cancer was detected concurrently with PNS in 49 (74.4%), before PNS in 13 (19.6%), and during follow-up after diagnosis of PNS in 4 (6%). We could identify more than one primary in 4 patients. Metastasis at the time of diagnosis occurred in 21.2% of those diagnosed to have malignancies. PCD was found to have a statistically significant association with carcinoma lung and ovary (p 0.04). A few representative images of Paraneoplastic syndromes with their associated tumors have been depicted in Figure-1.

Paraneoplastic antibody Profile

Antibodies were done in serum in 68 (70.1%) patients and detected in 52 (76.4%) of these patients. Well-characterized antibodies were found in 40 (76.9%), while partially characterised antibodies were detected in 12 (23.1%). Anti-Yo antibody and anti-Ma2 antibody were the most common antibodies found in 13 (25%) each. A statistically significant association was seen between anti-Yo antibody and PCD (p - 0.017). We also found an association of anti-Yo antibody with ovarian carcinoma (p - 0.03) and NMDAR antibody with ovarian teratoma (p - 0.0001).

Treatment

Among 66 patients with diagnosed tumors, all received

Table 3: Comparison of clinical-demographic profile and outcomes among the different subgroups

Variables	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	*P*-value
No of patients	10	20	9	12	24	22	
Age (Mean/SD)	55.7 (9.9)	56 (15.7)	54.3 (14)	43.7 (16.1)	57.3 (11.9)	51.5 (11.7)	0.67
Gender (M/F))	5/5	11/9	6/3	4/8	18/6	14/8	0.25
MRS (Mean/SD)	3.7 (0.9)	3.6 (0.5)	3.4 (0.5)	4 (0.9)	3.6 (0.6)	3.4 (0.6)	0.32
Time to diagnosis (months)	4.5 (3.1)	8.5 (13.3)	17 (15.7)	6.4 (8.2)	10.4 (12.3)	17.8 (16.5)	0.03
Temporal profile (Acute/subacute/chronic)	1/9/0	7/8/5	0/3/6	3/5/4	5/3/6	1/11/10	0.02
Good outcome with immunotherapy	2/4	9/10	4/4	6/9	10/13	11/16	0.88
Death (long term)	4	6	0	3	4	2	0.03
Metastasis	3	6	0	3	2	0	0.03
Prior diagnosis of tumor	3	3	0	3	4	0	0.48

Analysis of different variables in the six subgroups-Group 1 – Classic syndrome with tumor with antibody, Group 2 – Classic syndrome with tumor without antibody, Group 3 – Classic syndrome with antibody without tumor, Group 4 – Nonclassic syndrome with tumor with antibody, Group 5 – Nonclassic syndrome with tumor without antibody, Group 6 – Nonclassic syndrome with antibody without tumor

primary treatment for their malignancy. Thirty six patients (54.5%) received additional immunotherapy. In the subgroup (31 patients) of PNS without a detected tumor, 20 (64.5%) received immunotherapy. The medications in the entire cohort included corticosteroids (37, 38.1%), intravenous immunoglobulin (22, 22.7%), plasma exchange (3, 3.1%), cyclophosphamide (29, 29.8%) and rituximab (8,8.2%).

Follow-up and outcomes

At 6 month follow-up, 53 (54.6%) patients improved, 33 (34%) worsened, 6 (6.2%) remained status quo, and 5 (5.2%) died. The cause of death was the progression of malignancy in 2 patients and septicemia in 3 patients.

In the overall cohort, among the 56 patients who received immunotherapy, 42 (75%) patients showed a good outcome ($P < 0.0001$) after 6 months. In the subgroup with tumors, a good outcome was seen in 28/36 (77.7%) who received additional immunotherapy compared to 9/30 (30%) who received cancer treatment alone ($P < 0.0001$). The outcome was better in patients who had cell-surface antibodies, compared to intraneuronal antibodies. Patients with anti-NMDAR antibodies had a favorable outcome, whereas those with Anti-Yo and anti-Hu antibodies had significant functional disabilities, as shown in Figure 2.

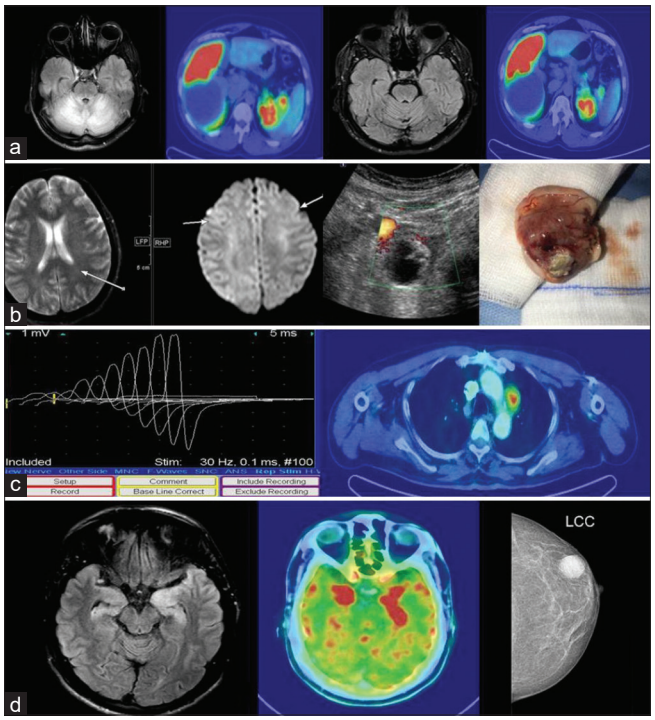

Figure 1: a) 37-year old man with subacute cerebellar ataxia and pancreatic neuroendocrine tumor with liver metastasis. MRI shows cerebellar swelling and hyperintensities; GA-68 DOTATATE-PET scan shows hypermetabolism in the tail of the pancreas and liver; treated with immunotherapy and Leutitium therapy for tumor. Repeat imaging after 1 year shows the disappearance of cerebellar hyperintensity with a mild reduction in metastasis. b) A 20-year old lady with NMDAR encephalitis; MRI shows nonspecific hyperintensities, Ultrasound abdomen-pelvis shows an ovarian mass, and gross section suggestive of ovarian teratoma. c) 40-year old smoker with fatiguability, diagnosed to have LEMS based on RNS showing incremental response at 30 Hz, PET CT shows lung metastasis-biopsy was suggestive of small cell carcinoma lung. d) 50-year old lady with limbic encephalitis; MRI shows medial temporal lobe hyperintensities; FDG-PET scan shows hypermetabolism in corresponding areas, and mammogram suggestive of breast malignancy

PNS's temporal profile, mRS <3 on presentation, treatment with immunomodulators, and absence of metastasis were statistically significant predictors of a good outcome on univariate analysis [Table 5]. All these factors, except mRS <3 on presentation, were also significant in multivariate analysis.

The mean duration of follow up was 24.3 months (SD-26.36). At the last follow-up, 34 (35.1%) patients had improved, 24 (24.7%) worsened, and 20 (20.6%) were lost to follow up. Deaths occurred in 19 (19.6%) patients. The predictors of mortality are given in Table 5.

The survival curve comparing outcomes of patients who received additional therapy with those who received only chemotherapy and patients with and without metastasis are shown in Figure 3.

Discussion

There is a shortage of high-quality studies on the clinical profile and outcomes of patients diagnosed with PNS, especially from the Indian subcontinent.[10–12] Majority of reported literature has been restricted to case series. Moreover, there is limited mention about the spectrum of nonclassical syndromes, morbidity, and therapeutic outcomes.

The main observations of this study include a high proportion of nonclassical neurological syndromes, multifocal neurological involvement, high functional disability at presentation, and improvement noted with immunotherapy. A broad spectrum of PNS, their onconeural antibody, and tumor associations have been depicted. The utility of a multimodality approach to detect tumors has also been emphasized.

Clinical and tumor profile

The relative distribution of disorders suggests paraneoplastic cerebellar degeneration, sensory-motor neuropathy, and encephalitis as the most frequently appearing PNS types. The clinical profile of various syndromes in our study was similar to the results of a previous European study involving 20 centers.[13] Previous Indian studies observed peripheral neuropathy and encephalitis as the most common PNSs.[10,11]

Lung and ovarian cancers were the most common cancers in our cohort. This was similar to other studies.[13,14] We observed that PCD is commonly associated with carcinoma of lung and ovary (p 0.04). Hematologic diseases were less prevalent than solid tumors in the present cohort. A metastatic spread was found only in 14 patients (21.2%), which supports the concept that PNS potentially facilitates an early diagnosis when the malignancy has limited spread.

The distribution of PNSs involving the central and peripheral nervous systems was similar. The symptoms of PNS preceded

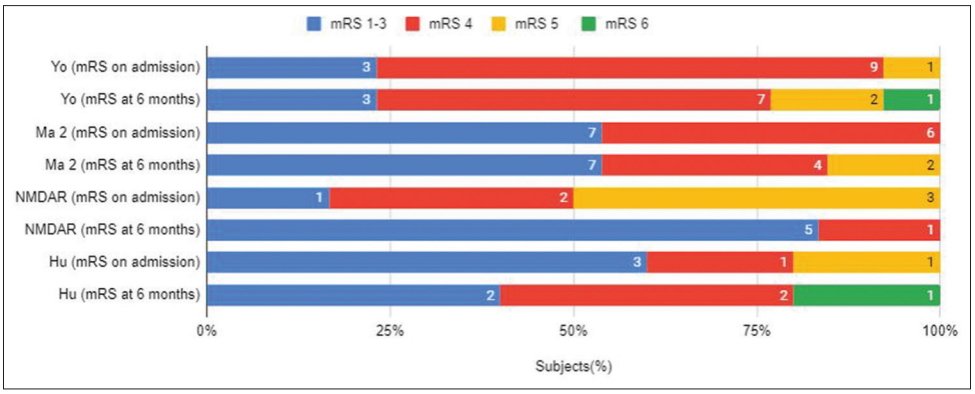

Figure 2: Comparison of modified Rankin Score (mRS) at admission and 6 months among common antibodies

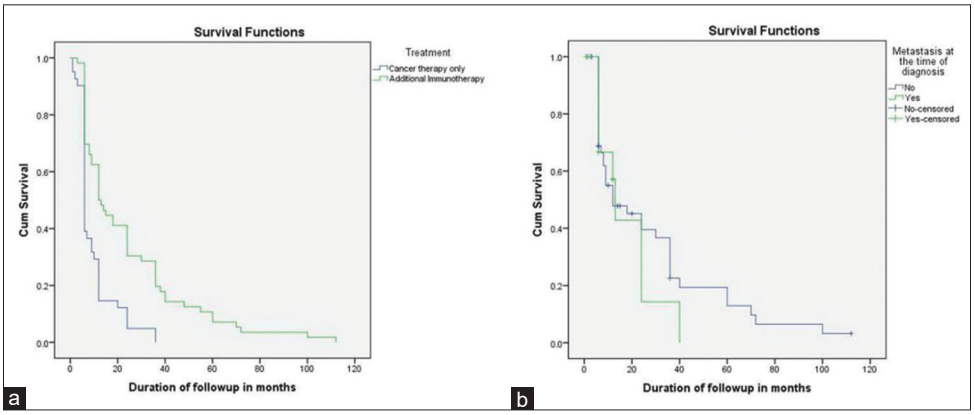

Figure 3: Kaplan Meier survival curve comparing outcomes of a) Patients who received additional immunotherapy with those who received only chemotherapy, b) Patients with and without metastasis at the time of diagnosis

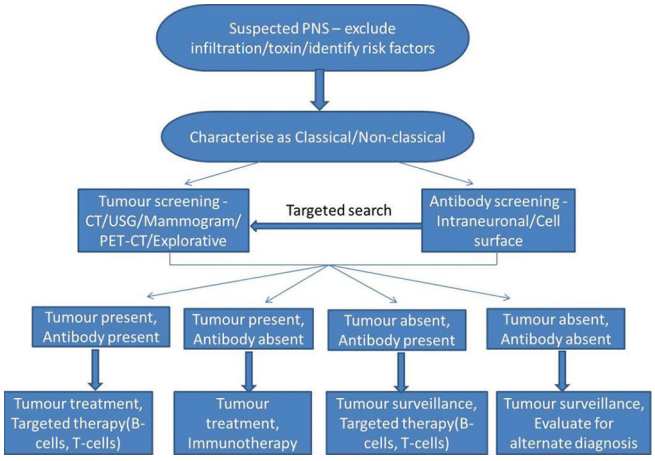

Figure 4: Algorithm for evaluation and management of PNS

the tumor symptoms in the majority of patients (75.7%). Therefore, a workup for paraneoplastic etiology is recommended in atypical, multifocal neurological syndromes with rapid progression. Early detection of tumors could have a massive impact on the overall course of the illness.

Onconeural antibody associations and relevance

Anti-Yo and anti-Ma2 antibodies were the most common antibodies. However, previous studies have observed anti-Hu antibody as the most common antibody.[13,15] PNS-antibody-tumor associations observed in the study included anti Yo antibody with PCD and ovarian carcinoma, and NMDAR antibody with ovarian teratoma. These observations, consistent with the previous literature,[5,16] have a role in facilitating a targeted search for malignancy.

We also found that patients with anti-Yo and anti-Hu antibodies were relatively refractory to treatment, whereas those with NMDAR antibodies showed significant functional improvement. This finding could be attributed to the differential immune responses implicated in cell surface antibodies compared with onconeural intracellular antigen-antibody interactions.

There were 31 patients without a diagnosed tumor but with a positive onconeural antibody. This subgroup of patients could be the ones in whom the cancer is yet to manifest or those who had a microscopic tumor that disappeared with a robust immune reaction.[4] The other explanation could be false-positive antibody tests. Low titers of antibody can rarely be seen in healthy individuals also.[17]

Meticulous tumor surveillance

Tumors are often too small to detect while still triggering an immune reaction.[4] A multimodality imaging search may

Table 4: Common malignancies and paraneoplastic antibodies associated with various PNSs

Paraneoplastic syndrome	Malignancy						Paraneoplastic antibody						
	Lung *n* = 13	Ovary *n* = 12	Lymphoma *n* = 6	Thymoma *n* = 5	Breast *n* = 5	Prostate *n* = 4	Yo *n* = 13	Ma 2 *n* = 13	NMDAR *n* = 6	Hu *n* = 5	SOX1 *n* = 5	CV2 *n* = 4	Amphiphysin *n* = 4
Cerebellar ataxia	6	6	0	0	0	0	6	1	0	4	1	1	0
Encephalitis	2	4	2	1	1	3	4	3	5	0	0	0	1
Neuropathy/ Plexus/DRG/ Root	4	1	1	0	1	0	1	4	0	0	3	1	2
Motor neuron disease	0	1	1	1	0	0	2	3	1	1	0	0	0
Neuromyotonia	0	0	1	3	1	0	0	0	0	0	0	1	0
LEMS	1	0	1	0	0	1	-	-	-	-	-	-	-
Others	0	0	0	0	2	0	0	2	0	0	1	1	1

Table 5: Predictors of good outcome and mortality

Predictors of a good outcome at the end of 6 months	Odds Ratio (95% Confidence interval)	*P*-Value
Age <40 years	1.37 (0.95 – 2.01)	0.14
Female sex	1.53 (0.84 – 2.51)	0.06
Temporal profile (acute, subacute)	1.34 (1.03 – 1.74)	0.02
Immunotherapy	8.18 (3.28 – 20.50)	0.0001
MRS <3 at presentation	1.88 (1.55 – 2.27)	0.04
Presence of malignancy	1.01 (0.68 – 1.48)	0.98
Absence of metastatic disease	1.18 (0.99 – 1.40)	0.03
Nonclassic syndrome	1.03 (0.71 – 1.48)	0.89
Positive Onconeural Ab	0.90 (0.30 – 2.73)	0.26
Definite PNS	1.14 (0.44 – 2.91)	0.79
Predictors of mortality (long term)		
Age >40 years	1.02 (0.76 – 1.37)	0.91
Male sex	1.44 (0.98 – 2.11)	0.08
Temporal profile (chronic)	1.08 (0.81 – 1.45)	0.16
Classic syndrome	1.66 (0.91 – 3.04)	0.11
Positive Onconeural Ab	1.33 (0.37 – 4.76)	0.58
Presence of malignancy	1.48 (1.13 – 1.92)	0.02
MRS ≥ 3 at presentation	1.25 (1.13 – 1.39)	0.38
Metastasis on diagnosis	2.77 (1.03 – 8.04)	0.04
Immunotherapy not given	1.33 (0.71 – 2.49)	0.27
Tumor diagnosis prior to presentation	1.47 (0.59 – 3.67)	0.08

be required to ensure the detection of tumors. PET scan was able to pick up an occult malignancy in 17 patients. There were several observations from our cohort where a targeted screen for tumors was successful. Mammogram and ultrasound of the testis for early detection of breast and testicular malignancy (Ma2 antibody-associated) respectively helped in diagnosis when advanced testing like PET was equivocal.

There was a patient with NMDAR encephalitis with a normal MRI of the pelvis, but ultrasound showing just increased echogenic changes in the right ovary. An ovarian teratoma was detected on laparotomy. The ovary's external appearance was normal; however, gross cut sections were suggestive of a teratoma, confirmed by histopathology. Again, this case emphasizes that the tumor is often not detected with standard imaging techniques and may warrant a combination of techniques or surgical exploration in situations with high clinical suspicion. This has to be considered even more strongly when the neurological symptoms are refractory to conventional treatment.

If the initial paraneoplastic screen is negative, a second screen should be performed 3-6 months later, followed by regular screening every six months for 5 years.[18] A search for the associated tumor has to continue if a tumor unrelated to a specific antibody is found. Onconeural antibodies could be a useful biomarker in addition to tumor surveillance in cases of PNSs. We had a patient in whom we diagnosed a recurrence of an ovarian tumor early because of the paraneoplastic cerebellar ataxia with a positive anti-Yo antibody. She was started on chemotherapy along with immunotherapy and showed significant improvement in symptoms and is still under follow-up.

Similarly, the presence of a refractory disease emphasizes the need for regular rescreening, as mentioned earlier. We readmitted another patient diagnosed with refractory inflammatory myopathy with a negative malignancy workup at the initial presentation, six months after discharge. A repeat paraneoplastic workup showed evidence of breast malignancy on the mammogram.

Role of immunotherapy in PNS

Literature shows that patients with positive cell surface antibodies usually respond better to immunotherapy than onconeural antibodies.[19] Previous studies have reported that irreversible neuronal damage and death are mediated by cytotoxic T-cells in patients with onconeural antibodies, explaining their inadequate response to treatment. However, two prospective studies suggest that immunomodulatory therapy in the appropriate patients can improve outcomes compared to the natural course of the disease.[20,21]

There was a definite improvement in functional status with adjuvant immunotherapy in our cohort. An accurate assessment of treatment efficacy for paraneoplastic neurological disorders is cumbersome due to the heterogeneity of clinical presentation and the low incidence of these disorders. Our study observed that immunotherapy benefits patients with both cell surface and intraneuronal (onconeural) antibodies, as evidenced by improvement in the mRS score by one at the end of 6 months. An acute or subacute presentation that leads to early diagnosis, mRS <3 on presentation, and absence of metastasis were predictors of a good outcome.

There are scarce systematic studies that mention the role of immunotherapy in PNS as an adjuvant to standard treatment of tumors. The need for multimodality treatment with IVIG/ Plasma exchange/steroids and cytotoxic therapy needs consideration. This could especially be useful in patients where the definitive treatment of the tumor is curative resection. The options will need to be tailored according to the type of tumor and the need for ongoing chemo-radiation. There is a case for continuing immunotherapy for the sake of improving neurological outcomes. Three studies had variable success using IVIG or IVIG in combination with methylprednisolone and cyclophosphamide[22–24]

Among the 53 patients who had initial improvement at the end of 6 months, the initial progress wore off during the subsequent follow-up visits in 19 patients. All these patients had evidence of tumor progression. This observation shows that the long term outcome is dependent mainly on tumor progression and its complications. Again, metastatic disease was significantly associated with overall mortality in the cohort.

Atypical presentations and PNS

Our cohort included a few patients with rapidly progressive motor neuron disease and atypical parkinsonism who satisfied the inclusion criteria for being a PNS based on the detection of an antibody/tumor. A chance association could explain the unusually high cases of motor neuron disease (10.3%) and atypical parkinsonism (6%) in our study compared to previous large studies. Paraneoplastic associations have been traditionally rarely described in this subset of disorders. The tendency of PET scan in identifying incidental tumors and the false positivity rates of onconeural antibody panel needs consideration in the setting of nonclassical syndromes. The tumor, if detected, will need definitive therapy as a standard of care. The neurological syndrome per se may warrant a trial of immunotherapy after treatment of the tumor in these cases. This may be especially applicable in cases with atypical presentation and rapid disease progression.

Limitations

Limitations include the retrospective nature of the study and the fact that treatment patterns were heterogeneous, often dictated by resource constraints. Antibody screening could not be done in all patients, especially during the early part of the study due to lack of availability.

Conclusion

A high index of clinical suspicion is essential for early diagnosis and prompt management of PNS. An algorithmic approach to management has been depicted in Figure 4. Paraneoplastic antibodies and a meticulous cancer screening play an important role in making an accurate diagnosis of PNS. Immunotherapy does have a role in improving the outcome of patients with PNSs.

Ethics approval (include appropriate approvals or waivers)

Approved by the Institutional Review Board, Christian Medical College, Vellore – IRB-11833 (Retro) and patient consent was waivered off.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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