

Various clinical features of patients with anti-Hu associated paraneoplastic neurological syndromes

An observational study

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Abstract

To describe and analyze the clinical features and prognosis of patients with anti-Hu associated paraneoplastic neurological syndromes (PNS).

The symptoms, MRI findings, cerebrospinal fluid (CSF) changes, electroencephalogram (EEG) characteristics and prognoses of 9 well-diagnosed anti-Hu associated PNS patients were analyzed.

The study enrolled 6 female and 3 male patients. Three patients presented with vertigo and 6 patients exhibited a depressed mood, numbness of the lower limbs, generalized pains, seizures, mental disturbances, and a temporary unilateral hand tremor on initial presentation. Three patients presented with MRI abnormalities localized in the mesial temporal lobe and the thalamus. Abnormal interictal EEG readings were observed in all 5 patients who underwent EEG study. Four patients were found lung cancer (3 during hospitalization, 1 during follow-up). Seven patients were treated with immunotherapy and improved in symptoms. Three patients died during follow-up (2 with lung cancer).

The clinical manifestation of anti-Hu associated PNS is diverse and multifocal. EEG may be more sensitive than MRI for early diagnosis of PNS. Long-term follow-up for patients with CT-negative anti-Hu associated PNS is necessary.

Abbreviations: CSF = cerebrospinal fluid, CT = computed tomography, EEG = electroencephalogram, GABA = gamma aminobutyric acid, MRI = magnetic resonance imaging, PCD = paraneoplastic cerebellar degeneration, PET = positron emission tomography, PLE = paraneoplastic limbic encephalitis, PNS = paraneoplastic neurological syndromes, SCLC = small cell lung cancer, SSN = subacute sensory neuropathy.

Keywords: anti-Hu, clinical features, paraneoplastic neurological syndromes, PNS

1. Introduction

Paraneoplastic neurological syndromes (PNS) are a group of immune-mediated neurological disorders that commonly occur with certain malignancies, such as small cell lung cancer (SCLC),^[1,2] breast cancer,^[3] thymoma,^[4] and lymphoma.^[5] Symptoms of PNS are highly diverse and usually precede manifestation of associated cancers,^[6] leading to difficulty in early diagnosis of PNS and a delay of intervention in the early stages of malignancy.

Over the past several decades, a dozen antibodies against antigens co-expressed by neurons and tumor cells have been identified. Detection of these antigens could be a potential diagnostic tool for PNS. These “onconeural” antibodies are found in approximately 60% of PNS patients, but their false positive rates for PNS are low.^[7] In the recommended diagnostic criteria set forth by the PNS Euro Network, patients presenting with neurological symptoms but without a detected cancer can be definitively diagnosed with PNS if well-characterized onconeural antibodies are detected.^[8] Anti-Hu is among the most well characterized of these antibodies and is most frequently seen in patients with PNS. About 2% of cancer patients are positive for anti-Hu, and these patients mostly have SCLC. Furthermore, detection of anti-Hu predicted a poorer prognosis for these patients.^[9] In recent years, novel interventions targeting the associated cancer or onconeural antibody-mediated injuries have been developed, which may significantly improve the prognosis of patients with PNS. Early identification of patients susceptible to PNS is vital. Because PNS is relatively rare in the clinical setting and the manifestations are diverse, there are limited reports on the clinical features of PNS patients and results among those reports are inconsistent.

In the present study, we described the clinical features and prognosis of 9 PNS patients who were positive for anti-Hu. We also reviewed the relevant literature concerning anti-Hu associated PNS.

2. Methods

In our retrospective study, we enrolled hospitalized patients at the Neurological Department of The First Hospital, Jilin

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University between March 2014 and October 2016. PNS patients whose serum or cerebrospinal fluid (CSF) sample was positive for anti-Hu antibody were enrolled. In addition to being positive for anti-Hu antibody, patients met all of the following criteria for study inclusion: presentation to the hospital with neurological complaints; exclusion of morbidity attributable to other neurological diseases that may cause symptoms similar to PNS; exclusion of tumor invasion or metastases to the central or peripheral nervous systems; and possession of a comprehensive medical record during hospitalization. According to the recommended diagnostic criteria,^[8] patients presenting with classical or nonclassical neurological symptoms and who tested positive for well-characterized onconeural antibodies, including anti-Hu, were definitively diagnosed with PNS in the absence of detected cancer. Therefore, all subjects enrolled in the present study fulfilled the requirements of definitive PNS diagnosis. Information regarding clinical features and responses to treatment were obtained based on completed medical records during hospitalization. Patients were followed-up via face-to-face interviews or telephone by experienced neurologists. Information regarding prognoses and further confirmation of associated cancers were obtained during the follow-ups.

The research protocol was approved by the First Hospital of Jilin University Medical Ethics Committee (No. 2014-304). The patient or guardian provided written or oral informed consent for all cases.

3. Results

A total of 9 patients were enrolled in the study, ranging in age from 37 to 71 years (mean age was 57 years). Six patients were female and 3 were male. Clinical features are summarized in Table 1.

3.1. Symptoms

Initial symptoms significantly varied among the 9 patients. Three patients initially presented with vertigo and the other 6 patients exhibited depressed mood, numbness of lower limbs, generalized pains, seizures, mental disturbances, and a temporary unilateral hand tremor. Another 2 patients developed seizures. Ataxia was noted in 3 patients, and paresthesias was noted in 2 patients. Neurological dysfunction preceded the manifestation of cancer-related signs in all 4 patients diagnosed with lung cancer. These 4 patients also differed from each other in initial symptomatology.

3.2. Laboratory tests

Lumbar puncture was performed in all patients. Six patients had a normal opening pressure, ranging from 105 to 180 mm H₂O. A slightly elevated opening pressure was observed in 3 patients (Cases 6, 8, and 9). An elevated white blood cell count ($208 \times 10^6/L$) was observed in 1 patient (Case 2). Three patients, including 1 with elevated white blood cells, had increased protein levels of 74.9, 67.8, and 59.6 mg/L. CSF onconeural antibodies were tested in 7 patients; all 7 patients were positive for anti-Hu

Table 1

Clinical features of 9 patients with anti-Hu-associated paraneoplastic neurological syndromes.

Patient no.	Gender/Age, years	Initial symptoms	Suspected lesion location*	MRI [‡]	CSF	Onconeural antibodies	Interictal EEG	NCV/EMG	Tumor/time [§]	Treatment/Outcome
1	F/58	Vertigo, disequilibrium	Brain stem, cerebellum	Negative	Negative	Anti-Hu(+)	None	None	Lung cancer/1 year	Supportive treatment/No improvement and died from lung cancer 15 months after discharge
2	F/37	Depressed mood	Limbic system	Left thalamus	Mild pleocytosis and elevated protein level	Anti-Hu(+) Anti-GABA(+)	Bilateral temporal area	None	Lung cancer/3 years	Immunoglobulin IV/Improvement in symptoms but died from lung cancer 6 months after discharge
3	F/46	Numbness of lower limbs	Dorsal ganglia	Right mesial temporal lobe, bilateral hippocampus	Negative	Anti-Hu(+)	Bilateral temporal area	Sensory neuropathy of lower limbs	Not found	Immunoglobulin IV/Improvement in symptoms
4	M/71	Generalized pain	Peripheral nerves? [†]	Negative	Negative	Anti-Hu(+)	None	Neurogenic injury of the limbs	Not found	Supportive treatment/No improvement at discharge but total recovery during following-up
5	F/65	Vertigo, nausea	Brain stem, cerebellum	Negative	Elevated protein level	Anti-Hu(+)	None	Neurogenic injury of the limbs	Not found	Methylprednisolone IV/Improvement in symptoms
6	F/59	Seizures	Brain stem, limbic system, lower motor neuron?	Negative	Elevated protein level	Anti-Hu(+) Anti-GABA(+)	Bilateral temporal area	None	Not found	Immunoglobulin IV plus dexamethasone IV/Improvement in symptoms and died from unknown causes 20 months after discharge
7	M/58	Vertigo, disequilibrium, diplopia	Brain stem	Negative	Negative	Anti-Hu(+)	None	None	Not found	Methylprednisolone IV/Improvement in symptoms
8	F/65	Blurred speech, depression, dullness	Limbic system	Bilateral hippocampus	Negative	Anti-Hu(+) Anti-Yo(+)	Bilateral temporal area	None	Lung cancer/60 days	Immunoglobulin IV/Improvement in symptoms
9	M/56	Temporal hand tremor	Limbic system, extrapyramidal system? [†]	Negative	Negative	Anti-Hu(+) Anti-GABA(+)	Left parietal-occipital-temporal area	None	Lung cancer/12 days	Immunoglobulin IV/Improvement in symptoms

* The determination of lesion localization was based on comprehensive evaluation during hospitalization.

[†] A“?” indicates uncertainty in the accuracy of localization.

[‡] The abnormalities were seen as a hyperintense signal on FLAIR or T2 imaging.

[§] The time interval between onset of neurological symptoms and diagnosis of tumor.

CSF=cerebrospinal fluid, EMG=electromyography, F=female, NCV=nerve conduction velocity, M=male.

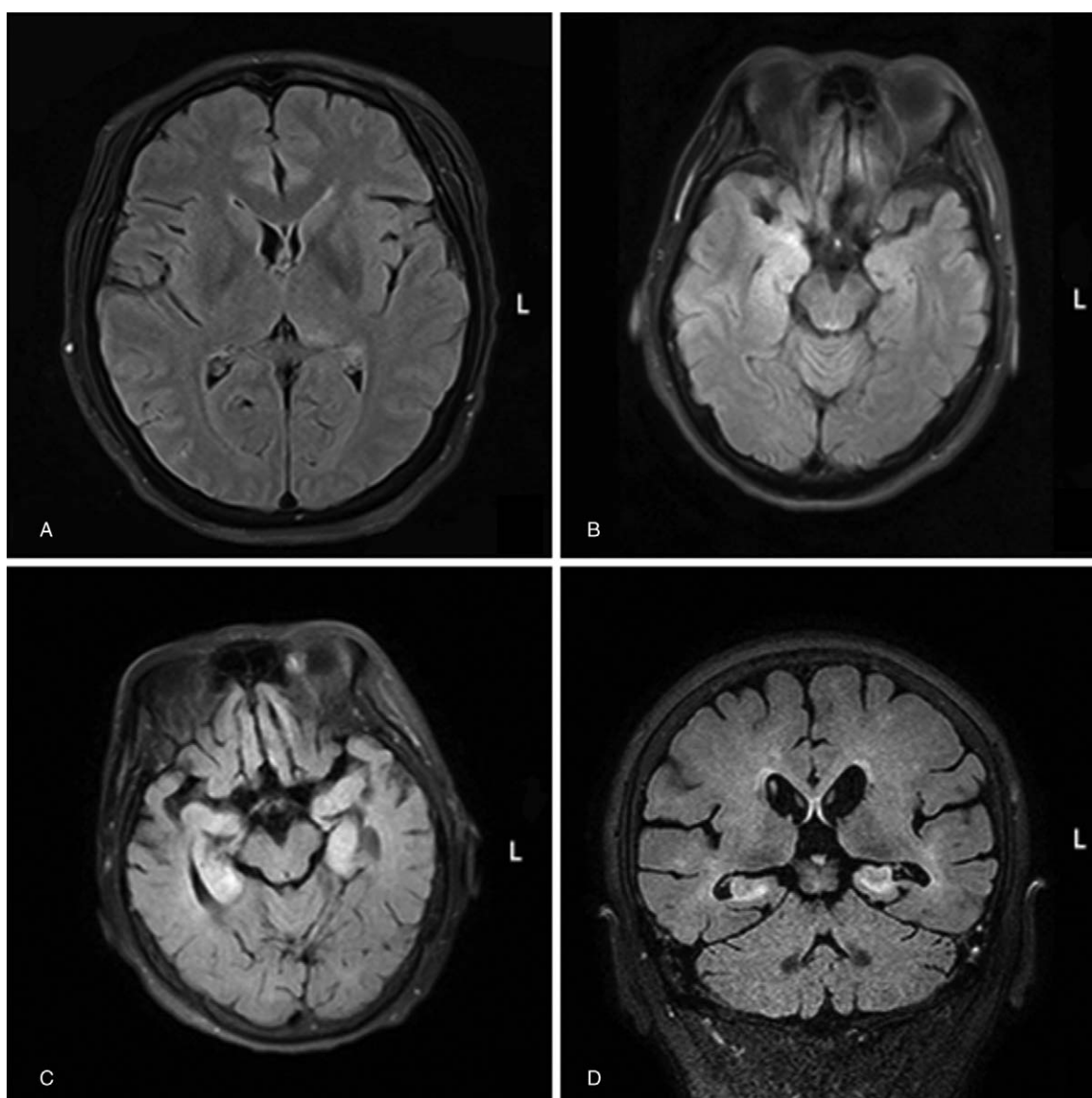


Figure 1. MRI (FLAIR) findings in 3 patients. (A, axial) Left thalamus hyperintensity in Case 2. (B, axial) Right mesial temporal lobe and bilateral hippocampus hyperintensity in Case 3. (C, axial) Bilateral hippocampus hyperintensity in Case 8. (D, coronal) Bilateral hippocampus hyperintensity in Case 8. EEG= electroencephalogram, MRI=magnetic resonance imaging.

in 7 patients 2 were positive for anti-gamma aminobutyric acid (GABA). Serum onconeural antibodies were also examined in all patients. Positive detection of serum anti-Hu, anti-GABA, and anti-Yo was observed in 9, 3, and 1 patients, respectively.

3.3. Neuroimaging

Brain magnetic resonance imaging (MRI) was performed in 9 patients. Three patients exhibited significant hyperintensity on FLAIR or T2-weighted imaging. In Case 2, the abnormality was localized to the left thalamus (Fig. 1A); this patient initially presented with a depressed mood and later manifested with seizures. The patient with numbness of the lower limbs (Case 3) had abnormalities in the right mesial temporal lobe and bilateral hippocampus (Fig. 1B). Case 8 also presented with initial symptoms of mental disturbances and MRI revealed bilateral abnormalities in the hippocampus (Fig. 1C and D). Two-thirds of the patients diagnosed with lung cancer had MRI abnormalities (Cases 2 and 8).

3.4. Electroencephalogram (EEG) and nerve conduction study

EEG was performed in 5 patients. All patients, including 2 patients without signs of epileptic episodes (Cases 3 and 8), demonstrated regional EEG abnormalities. Most patients exhibited interictal sharp or spike discharges with slow waves in the bilateral temporal area (Fig. 2). Details of EEG patterns of each patient are summarized in Table 1. Nerve conduction studies (summarized in Table 2) confirmed dysfunction of peripheral nerves in 3 patients exhibiting symptoms or signs of peripheral neuropathy (Cases 3, 4, and 5).

3.5. Detection of associated tumors

Anti-Hu is typically associated with SCLC. Chest computed tomography (CT) scan was performed in all 9 patients to detect possible tumors during hospitalization. In the initial CT scan, 3 patients had focal lesions in the lungs (Cases 2, 8, and 9),

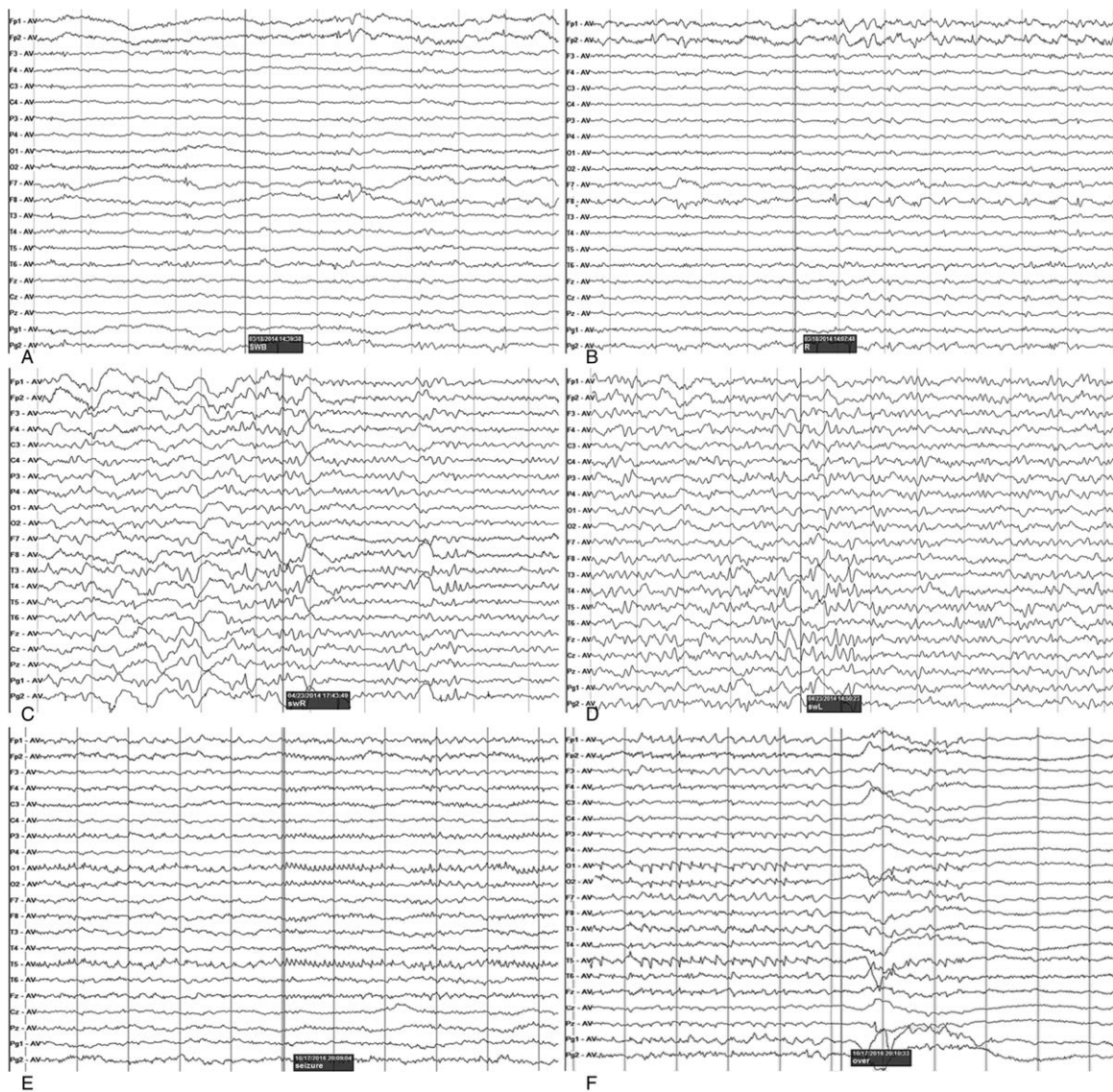


Figure 2. Interictal EEG findings in 5 patients. (A, B) Sharp discharges with slow waves in the bilateral temporal area were seen in Case 3. (C, D) Sharp discharges with slow waves and arrhythmic δ waves were seen in the bilateral temporal area in Case 6. (E, F) A decrease in background amplitude and sharp discharges exclusively localized to the left temporal area, as well as an abnormal focal discharge in the left occipital-temporal area, was seen in Case 9. EEG = electroencephalogram.

Table 2
Nerve conduction study of 3 patients.

	Conduction velocity			Latency			Amplitude		
	Case 3	Case 4	Case 6	Case 3	Case 4	Case 6	Case 3	Case 4	Case 6
Sensory nerve conduction									
Ulnar nerve	Normal	Normal		Normal	Normal		Normal	Normal	
Median nerve	Normal	Normal		Normal	Normal		Normal	Normal	
Sural nerve	Unrecorded	Reduced	Unrecorded	Unrecorded	Normal	Unrecorded	Unrecorded	Normal	Unrecorded
Superficial peroneal nerve	Unrecorded	Normal	Unrecorded	Unrecorded	Normal	Unrecorded	Unrecorded	Normal	Unrecorded
Motor nerve conduction									
Ulnar nerve	Normal	Normal		Normal	Normal		Normal	Normal	
Median nerve	Normal	Normal		Normal	Normal		Normal	Normal	
Common peroneal nerve	Normal	Reduced	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Tibial nerve	Normal	Reduced	Normal	Normal	Normal	Normal	Normal	Normal	Normal

suggesting the existence of an associated tumor. Lung cancer was further confirmed by positron emission tomography (PET)-CT scan in 1 (Case 8) of these 3 patients. One other patient (Case 1) was diagnosed with lung cancer during follow-up. No histological examination of the tumors was performed during hospitalization or follow-ups. The time interval between onset of neurological symptoms and the diagnosis of lung cancer in the 4 patients was 1 year, 3 years, 2 months, and 12 days. Four patients with negative chest CT results underwent abdominal ultrasonography and no abnormalities were found.

3.6. Treatment and outcomes

On admission, only 1 patient (Case 6) was diagnosed with PNS. The details of initial diagnosis and treatment of each case are presented in Table 1. Immunotherapy (steroids and/or intravenous immunoglobulin) was administered to 7 patients after PNS diagnosis. Cases 1 and 4 refused to undergo immunotherapy and were administered supportive treatment. Duration of patient hospitalization ranged from 9 to 40 days. All 7 patients who underwent immunotherapy showed some improvements at discharge, and 5 of the 9 patients were followed-up after discharge. Case 1, who was newly diagnosed with lung cancer 11 months after onset, died after 15 months of follow-up. Case 2 died of lung cancer at 6 months after discharge. Cases 3 and 4 remained stable in disease severity until 12 months after discharge without tumor-associated manifestations. Case 6 died at 20 months after discharge; the cause of death was unclear and no evidence of an associated tumor was found based on autopsy.

4. Discussion

In the 1950s, the term “paraneoplastic” was first used to describe neurological disturbances likely to be associated with tumors by mechanisms other than tumor metastasis and invasion into the nervous system, metabolic dysfunction, infection, or side effects of cancer treatment.^[10] The disease is now recognized as immune mediated.^[11] In the context of certain malignancies, a neural cell-specific antigen is ectopically expressed by tumor cells, leading to the production of auto-antibodies against neural cells and contributing to cytotoxic T cell-mediated inflammatory injuries throughout the nervous system.^[12,13] Although these onconeural antibodies do not directly contribute to the pathogenesis of PNS, they are reliable serum and CFS biomarkers for accurate diagnosis of the condition.^[14] According to the current diagnostic criteria of PNS, patients’ positive for well-characterized onconeural antibodies can be definitively diagnosed with PNS in the absence of an identified tumor.

Anti-Hu antibody is among the most well characterized of the onconeural antibodies.^[15] Physiologically, anti-Hu is expressed in the nuclei of neurons, functioning as an RNA-binding protein that plays a crucial role in neural development.^[16] In the original study by Graus et al,^[17] anti-Hu antibody was first identified in 2 patients comorbid for subacute sensory neuropathy (SSN) and SCLC. Anti-Hu has also been reported in a large number of patients with various neurological disturbances, including limbic encephalitis,^[18,19] brainstem encephalitis,^[19] chronic gastrointestinal pseudo-obstruction,^[20] and paraneoplastic cerebellar degeneration (PCD).^[21] Although anti-Hu antibodies have been observed in patients with a variety of extra thoracic cancers, it is highly specific for lung cancer, especially SCLC. It is estimated that approximately 85% of anti-Hu positive cases are associated with SCLC.^[11] In a study enrolling 200 anti-Hu-associated

patients with PNS, lung cancer was observed in 144 (85.6%) cases, with 111 cases confirmed as SCLC by histology. Only 23 (14.4%) cases were found to have extra thoracic cancers, such as prostate, breast, gastrointestinal, bladder, and ovarian cancer.^[9] Another study found that SCLC accounted for 94% of cases in 50 patients diagnosed with anti-Hu associated paraneoplastic limbic encephalitis (PLE).^[10] In the current study, only 4 cases of the 9 anti-Hu associated PNS patients had lung cancer; this proportion is significantly lower than that in previous reports. This inconsistency may be attributed to the following reasons: First, in the current study, patients may have been enrolled at a relatively earlier stage of disease, resulting in the cancer being difficult to identify with conventional diagnostic techniques. Most previous studies were conducted more than a decade ago; our awareness of and knowledge about PNS have significantly increased during the past 10 years. This has allowed a greater number of patients with suspected PNS to be evaluated for malignancies prior to overt manifestation. In our study, only 2 patients with negative CT scans were further examined by PET-CT. Additionally, follow-up durations remained relatively short in our study, and CT or PET-CT scan was not routinely repeated during follow-up. It is estimated that an associated cancer may not emerge until 4 to 5 years after the occurrence of neurological syndromes; thus, we cannot rule out the possibility that false-negative results were observed in some patients. Secondly, the small sample size in the current study may contribute to inconsistencies with previous reports.

The gender ratio in anti-Hu-positive PNS patients was inconsistent among previous reports. Graus et al^[9] found that male patients accounted for 75.5% cases in a European population. However, in a study of an American population, Lucchinetti et al^[22] found that 67% of anti-Hu positive cases were females, which was similar to that reported by Dalmau et al.^[15] Graus et al argued that the inconsistency may be attributed to the difference in gender distribution among SCLC in these countries. In the current study, the number of female patients is twice that of male patients. Although results may be influenced by the relatively small sample size, these findings could indicate an association of SCLC incidence in the Chinese female population.

The clinical features of PNS are highly diverse, and the disease can affect both the peripheral and central nervous systems. Multifocal manifestations are most frequently observed. Dalmau et al^[23] reported occurrence of symptoms associated with the cerebellum (25%), sensory pathways (54%), motor pathways (45%), brain stem (31%), autonomic nerves (28%), and limbic system (22%) in PNS cases. Gultekin et al^[10] found that 78% of anti-Hu-positive patients exhibited multifocal neurological symptoms. Similar results were reported by Graus et al,^[9] in that 70% of cases exhibited multifocal involvement upon PNS diagnosis. However, a predominant neurological syndrome was observed in approximately 60% of cases during clinical evaluation. The most frequent dominant neurological syndrome at diagnosis was sensory neuropathy, followed by cerebellar ataxia, cortical encephalitis, brain stem encephalitis, sensory motor neuropathy, and dysautonomia.^[9] In our 9 cases, 6 patients exhibited neurological symptoms associated with at least 2 different levels of the nervous system at disease onset; the remaining 3 patients exhibited symptoms confined to single neuroanatomical areas. This suggests that PNS can affect multifocal areas in its early stages. A thorough neurological examination is required to localize neurological dysfunction.

The typical MRI manifestation of PNS is a hyper-intense signal on T2-weighted image, usually restricted to the mesial temporal lobe, reflecting a focal inflammation in the central nervous system.^[24] Only 3 of our cases exhibited an MRI image typical for PNS. The frequency of MRI abnormalities was lower than that in previous studies. One study showed that 64% of patients positive for anti-Hu were comorbid for PLE.^[10] Another study found that 54% of cases in a population of anti-Hu encephalitis exhibited MRI abnormalities.^[25] The lower frequency of MRI abnormalities in our study may be attributed to the difference in clinical features of the studied population. The 2 aforementioned studies only enrolled patients with symptoms indicating cortical involvement, but in our study, we enrolled patients with cortical symptoms as well as those with isolated spinal or peripheral nervous dysfunction. Of note, 1 patient (Case 3) with suspected isolated sensory neuropathy manifested with unilateral temporal lobe involvement, and 4 patients (Cases 1, 5, 6, and 7) manifested with symptoms indicating brain stem or cerebellar dysfunction, but exhibited no findings upon MRI. These findings suggest that brain MRI could be useful for identifying subclinical cortical lesions but less effective for lesion localization to the brain stem or cerebellum.

Several cases in our study revealed mild pleocytosis and elevated protein and IgG concentration in the CSF, consistent with previous reports.^[18] This suggests that abnormalities in the CSF are nonspecific for PNS, and findings should be used for the purpose of excluding other neurological disorders with symptoms similar to PNS, such as intracranial infection, multiple sclerosis, and malignant meningioma. In previous studies, EEG was found to be of limited diagnostic value for PNS.^[9] However, in our study, abnormal activity restricted to bilateral temporal areas was most frequently affected in PNS, and was observed in all 5 patients that underwent EEG investigation. Two of these 5 patients (Cases 4 and 9) had no significant findings upon MRI, suggesting that EEG may be more sensitive than MRI in identifying early central nervous system abnormalities in the setting of PNS.

Prognosis of PNS with anti-Hu antibodies is thought to be poor in general.^[6,11] Interventions for this condition include immunotherapy and the treatment of associated tumor. Our study, as well as previous studies, report PNS patients with anti-Hu antibodies to respond to immunotherapy using intravenous immunoglobulin or steroids.^[11] In the 3 patients (Cases 2, 6, and 9) who presented with altered consciousness on admission remission from seizures was noted after immunotherapy was initiated; although it should be noted that no improvement in consciousness was observed. The 2 patients (Cases 1 and 4) who did not agree to immunotherapy showed no improvement at discharge. These data suggest that the most effective treatment for improving symptoms of PNS is the treatment of the associated tumor itself.^[9,11] However, for a considerable proportion of patients, the associated tumor may not be identified until it is late stage, and either radiochemical therapy or surgical intervention could significantly improve the outcome of patients on diagnosis. The early diagnosis of PNS as well as any associated tumors is obviously imperative. Patients positive for anti-Hu but exhibiting no significant findings on chest CT scan at initial evaluation should be examined for associated tumors using more sensitive diagnostic techniques, such as PET-CT, or having a repeat CT scan during following-up.

In conclusion, we found that in the Chinese population of patients with anti-Hu associated PNS, the frequency of underlying tumors may be lower than that in Caucasian

populations, but this requires further confirmation by studies with larger sample sizes. We report that PNS is diverse in symptomatology and neurological involvement is usually multifocal. Brain MRI is useful for identifying subclinical cortical lesions instead of brain stem or cerebellar lesions; however, MRI utility is limited by low specificity. EEG may be more sensitive than MRI in revealing early central nervous system abnormalities, and thus EEG should be routinely performed on all patients suspected to suffer from PNS.

Author contributions

Data curation: Jia Li.

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Writing – original draft: Jia Li.

Writing – review & editing: Weihong Lin.

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