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Paraneoplastic Neurologic Syndromes: Rare But More Common Than Expected Nine Cases with a Literature Review

Paraneoplastik Nörolojik Sendromlar: Nadir Ancak Beklenenden Daha Sık Dokuz Olgu ile Literatür Derlemesi

Hülya Uluğut Erkoyun, Sevgin Gündoğan, Yaprak Seçil, Yeşim Beckmann, Tülay Kurt İncesu, Hatice Sabiha Türe, Galip Akhan

Izmir Katip Celebi University, Atatürk Training and Research Hospital, Department of Neurology, Izmir, Turkey

Abstract

Paraneoplastic neurologic syndromes (PNS) are rare disorders, which are remote effects of cancer that are not caused by the tumor, its metastasis or side effects of treatment. We had nine patients with PNS; two of our patients had limbic encephalitis, but one had autoimmune limbic encephalitis with no malignancy; two patients had subacute cerebellar degeneration; three had Stiff-person syndrome; one had Lambert-Eaton myasthenic syndrome; and the remaining patient had sensory neuronopathy. In most patients, the neurologic disorder develops before the cancer becomes clinically overt and the patient is referred to a neurologist. Five of our patients' malignancies had been diagnosed in our clinic after their neurologic symptoms became overt. PNS are more common than expected and neurologists should be aware of the variety of the clinical presentations of these syndromes. When physicians suspect PNS, cancer screening should be conducted. The screening must continue even if the results are negative.

Keywords: Paraneoplastic, neurologic syndromes, neurogenic autoantibodies

Öz

Paraneoplastik nörolojik sendromlar (PNS), kanserin doğrudan, metastaz ya da tedavi yan etkisine bağlı olmayan, uzak etkisi ile ortaya çıkan nadir hastalıklardır. Dokuz PNS'li hastanın ikisi limbik ensefalitti fakat bunlardan biri otoimmün limbik ensefalitti ve malignitesi yoktu. İkisi subakut serebellar dejenerasyon, üçü Stiff-person sendromu, biri Lambert-Eaton miyastenik sendromu diğeri ise duyusal nöronopatiydi. Birçok hastanın nörolojik bulgusu kanserden önce gelişir ve nöroloğa yönlendirilir. Bizim de beş hastamız malignite tanısını bizim kliniğimizde aldı. PNS sanılandan daha sıktır ve nörologlar bu sendromları akılda bulundurmalıdır. PNS'den şüphelenildiğinde mutlaka kanser taraması yapılmalı ve sonuçlar negatif gelse de tarama sürdürülmelidir.

Anahtar Kelimeler: Paraneoplastik, nörolojik sendromlar, nörojenik otoantikorlar

Introduction

Paraneoplastic neurologic syndromes (PNS) are rare disorders, which are remote effects of cancer that are not caused by the tumor, its metastasis or side effects of treatment (1). Whereas some syndromes affect only certain parts of the nervous system, other syndromes involve both central and peripheral neurons, resulting in complex clinical manifestations. The most common cancer associated with PNS is small-cell lung cancer (SCLC) (2). Many other cancer types are also associated with PNS. PNS can cause severe disability and can even be fatal. Survival is related with both oncologic disease and PNS. The recognition and diagnosis of PNS are very important in neurology practice. Herein, we present nine patients with PNS who were followed up in our neurology clinic in the last two years and we review the findings in light of the literature.

Case Reports

We had nine patients with PNS; two patients had subacute cerebellar degeneration (SCD); three had Stiff-person syndrome (SPS); one had Lambert-Eaton myasthenic syndrome (LEMS); and the remaining patient had sensory neuropathy (SN). Case summaries are given in Table 1. All PNS autoantibody tests were evaluated in Dokuz Eylul University neuro-immunology

Address for Correspondence/Yazışma Adresi: Hülya Uluğut Erkoyun MD, Izmir Katip Celebi University, Atatürk Training and Research Hospital, Department of Neurology, Izmir, Turkey
Phone: +90 505 616 75 80 E-mail: hulyaerkoyun@gmail.com ORCID ID: orcid.org/0000-0002-5016-2505
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laboratory. Informed consent was taken from all patients in line with the Declaration of Helsinki.

Subacute Cerebellar Degeneration

SCD is characterized by subacute development of severe pancerebellar dysfunction. Cerebellar signs usually begin with gait ataxia and, after a few weeks or months, progress to severe, usually symmetrical truncal and limb ataxia, with dysarthria and often nystagmus (3). Preferentially associated tumors are listed in Table 2.

Case 1

A ninety-year-old woman was admitted to our clinic with vertigo, dysarthria, and dysphagia, which she had had for three days. There was nothing except hypertension in her medical history. The patient had vertical upper gaze palsy, dysarthria, bilateral decreased gag reflex, bilateral dysmetria, gait ataxia, and bilateral positive Babinski sign in the neurologic examination. We found no significant data in supporting diagnostic tests (Table 3). However, we detected bilateral conduction block in the fasciculus gracilis in somatosensory evoked potentials (SEP). High protein levels were detected in the cerebrospinal fluid (CSF). The patient was suspected to have SCD, possibly due to the presence of a latent malignant tumor. Anti-Yo antibody was positive in the serum. Gadolinium computed tomography (CT) was performed to survey the whole body and a metastatic axillary lymph node (2-2.5 cm) was discovered. The histologic diagnosis of the axillary lymph node biopsy was malignant epithelial tumor metastasis. We screened for the primary tumor. We consulted the oncology clinic for the patient. A biopsy from the left breast was malignant. They did not advise chemotherapy to our patient because of her age.

Case 2

A fifty-six-year-old woman was admitted to our clinic with loss of balance, dyspnea, and extremity weakness. She had had left-sided pain in her chest for two months. Later, she had burning and contractions in her legs. These symptoms continued and she became unable to walk. In the neurologic examination, she had horizontal and rotatory nystagmus while looking to the left-side and right-side horizontal nystagmus. Flexion of neck muscle strength was 4+/5. She had glove-stocking-type sensation disorder with hyperalgesia. Vibration sensation was lost in all extremities. Deep tendon reflexes (DTR) were hypoactive in upper extremities and lost in lower ekstremities. The Babinski sign was positive on the right-side. She had dysmetria, dysdiadochokinesia, and clumsy knee-heel test bilaterally. Gait ataxia was prominently positive on the right side. Her walking was also ataxic and we occasionally witnessed myoclonus. Supportive diagnostic tests are summarized in Table 3. The patient was suspected to have SCD. Her anti-Hu antibody was positive but the GQ1b (for the exclusion of Miller-Fisher syndrome) antibody was negative in paraneoplastic screening tests. We administered 0.4 g/kg/day intravenous immunoglobulin (IVIG). She did not improve significantly. Then we administered 1 g/day pulse steroid therapy. She benefited moderately from the pulse steroid therapy. The patient was taken to neurological intensive care unit because of the progression of dyspnea. We

Table 1. Data of patients

Case	Age	Sex	Paraneoplastic neurological syndromes	Main associated tumors	Paraneoplastic antibodies
1	90	F	Subacute cerebellar degeneration	Breast	Anti-Yo
2	56	F	Subacute cerebellar degeneration	Small-cell lung cancer	Anti-Hu
3	63	M	Stiff-person syndrome	Not detected	Anti-GAD
4	57	F	Stiff-person syndrome	Thyroid	Anti-GAD
5	44	F	Stiff-person syndrome	Breast	Not evaluated
6	60	M	Lambert-Eaton myasthenic syndrome	Small-cell lung cancer	Not evaluated
7	53	M	Sensory neuronopathy	Lung adenocarcinoma	Anti-Yo
8	56	M	Limbic encephalitis	Testicle	Negative
9	54	M	Limbic encephalitis	No tumor	LGI1

F: Female, M: Male, LGI1: Leucine-rich glioma inactivated 1, GAD: Glutamic acid decarboxylase

Table 2. Supportive diagnostic tests in patients with subacute cerebellar degeneration

Case	CSF	Brain MRI	EEG	Evoked potentials	EMG
1	Protein: 71 mg/dL Cytology: N Culture: N	Bilaterally periventricular chronic ischaemic lesions	N	Bilaterally block in fasciculus gracilis in SEP	N
2	Protein: 146 mg/dL Cytology: N Culture: N	N (brain and cervical)	N	Bilaterally conduction elongated in VEP, bilaterally block in fasciculus gracilis and cuneatus in SEP	Axonal-demyelinating sensory motor PNP

CSF: Cerebrospinal fluid, EEG: Electroencephalography, EMG: Electromyography, PNP: Polyneuropathy, SEP: Somatosensory evoked potential, MRI: Magnetic resonance imaging, N: Normal, VEP: Visual evoked potentials

consulted the chest diseases clinic with positive anti-Hu antibody and thorax CT results. Her fine needle aspiration biopsy revealed SCLC. She was referred to the chest disease clinic for treatment.

Stiff-person Syndrome

SPS is rare neurologic disorder characterized by stiffness more prominent in axial muscles, with co-contraction of agonist and antagonist muscle groups, and painful spasms precipitated by sensory stimuli. Electromyography (EMG) revealed the existence of continuous motor unit activity in the affected muscles at rest (4). The paraneoplastic variant of SPS is associated with breast cancer in women (Table 2).

Case 3

A sixty-three-year-old male patient was admitted to our clinic with progressive stiffness in his legs, which had developed over two years. His symptoms had increased gradually in the last two weeks. There was benign prostate hypertrophy in his medical history. There was bilateral spasticity in his lower extremities and axial body muscles in the neurologic examination. Continuous muscle fiber activity was seen in agonist and antagonist muscles in EMG. Glutamic acid decarboxylase (GAD) antibody was positive. We diagnosed SPS. Baclofen and diazepam were administered for symptomatic treatment. We wanted to screen the patient for the main associated tumor but he did not accept the advanced investigation.

Case 4

A fifty-seven year old female patient with known papillary thyroid cancer was admitted to our clinic with progressive difficulty in walking which was developed in six months. Her EMG that was performed previously indicated that she had SPS. In neurological examination, her DTRs were increased, had spasticity in her legs bilaterally. Her Achilles reflex could not have been evaluated because of spasticity. No motor deficit was seen. EMG was performed again and spontaneous motor unit potentials were seen especially in para-spinal muscles. Her GAD antibody titer was over 2000 units so we have diagnosed the patient as SPS. We screened neoplasia for overlap malignancy but nothing was detected except calcifications in breast. Mammography was reported BIRADS 2. Breast surgeons offered follow-up of patients. She still has been in our follow up and we didn't detect any malignancy except papillary thyroid carcinoma. We administered diazepam and increased dose slowly. She still has been administered IVIG therapy. She benefitted fairly but her complaints have not been resolved completely.

Case 5

A forty-four-year-old female patient was admitted to our clinic with stiffness in her extremities, which she had had for a year. She had been administrated various drugs such as gabapentin, clonazepam, and antidepressants in other hospitals. She had not

Table 3. Main paraneoplastic neurological syndromes and associated antibodies*

Paraneoplastic neurological syndromes	Main associated tumors	Main frequent associated paraneoplastic antibodies	Frequency of paraneoplastic origin
Limbic encephalitis	Small-cell lung cancer Testicular	Hu-Ab CV2-Ab Ma2-Ab Amphiphysin-Ab	20%
Subacute cerebellar ataxia	Ovary, breast Small-cell lung cancer Hodgkin's disease	Yo-Ab Hu-Ab CV2-Ab Tr-Ab Ma-Ab	50%
Lambert-Eaton myasthenic syndrome	Small-cell lung cancer	VGCC-Ab	60%
Sensory neuropathy	Small-cell lung cancer	Hu-Ab CV2-Ab	20%
Stiff-person syndrome	Breast	Amphiphysin-Ab	20%
Opsoclonus myoclonus	Neuroblastoma, breast, lung	Hu-Ab Ri-Ab	20%
Encephalomyelitis	Small-cell lung cancer	Hu-Ab CV2-Ab Amphiphysin-Ab Ma2-Ab	10%
Chronic gastrointestinal pseudo obstruction	Small-cell lung cancer	Hu-Ab CV2-Ab	-
Retinopathy	Small-cell lung cancer Melanoma	Recoverin-Ab CV2-Ab Rod-bipolar-cell-Ab	-

*Honnorat J, Antoine JC. Paraneoplastic neurological syndromes. Orphanet J Rare Dis 2007;2:22.

benefited from these drugs. She was admitted for further assessment. There was severe spasticity in her all limbs and neck. Bilateral Babinski signs were positive. DTRs were increased. Continuous muscle fiber activity was seen in muscles in EMG. Together with all of these findings, we diagnosed the patient as having SPS. We administered a baclofen pump to her. We scanned for neoplasia. A mass lesion was detected in the right breast in a mammography. Invasive ductal carcinoma was diagnosed in biopsy material. The oncology department planned chemotherapy after surgery. In her follow-up, brain and bone metastases occurred. The oncology department added radiotherapy to her treatment protocol. Her neurologic condition had progressed. Motor weaknesses was 3/5 in all limbs. Spasticity was relieved. In her last clinic evaluation, liver metastases were diagnosed. Her follow-up continues in our clinic and oncology clinic.

Lambert-Eaton Myasthenic Syndrome

LEMS is an autoimmune disorder of the neuromuscular junction characterized by muscle weakness and autonomic dysfunction. After high frequency (more than 20 Hz) stimulation, a near-100% increment response is very characteristic on repetitive nerve stimulation test on EMG (4). Almost 60% of patients with LEMS are paraneoplastic and SCLC is the main associated cancer (Table 2).

Case 6

A sixty-year-old man with a 2-month history of swallowing difficulty was admitted to our clinic. He had pneumonia and was taking antibiotherapy for it. His symptoms had not been relieved and he had difficulty in walking for 20 days. He was unable to do his daily activities and climb up stairs. He had no disease history except hyperlipidemia. In the neurologic examination, his muscle strength was 3-4/5 in the lower extremities and the loss was predominantly in the proximal and extensor regions. Cranial nerves, touch sensation, and positioning were normal. His DTRs were hypoactive. An increment response was observed in his right trapezius muscles in the fast repetitive stimulation test in EMG (Figure 1). These findings were considered in accordance with LEMS. He had bronchoscopy after thorax CT. His biopsy revealed SCLC. No metastases were detected. He was referred to a chest hospital.

Sensory Neuronopathy

SN is characterized by primary damage of the sensory nerve cell body of the dorsal root ganglia. The main clinical symptoms at onset are pain and paresthesias with asymmetric distribution

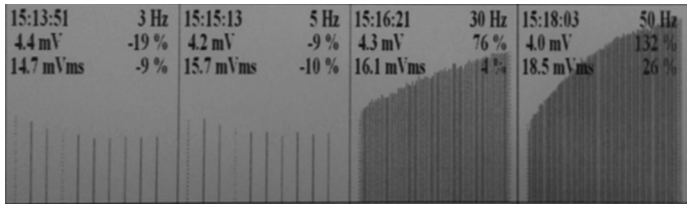


Figure 1. Patient 6, who was diagnosed as having Lambert-Eaton myasthenic syndrome with small-cell lung cancer. Increment response was observed in his right trapezius muscles in the repetitive stimulation test

that involves the arms rather than the legs (4). The main associated tumors are listed in Table 2.

Case 7

A fifty-three-year-old male patient was admitted to our clinic with numbness in his hands and feet, which he had had for 1 month. There was prostate carcinoma in his family medical history. There were short glove-stocking sensory and vibration loss in his neurologic examination. His DTR were normal. We detected axonal SN in the EMG. There was bilateral conduction block in the fasciculus gracilis and bilateral conduction elongation in the fasciculus cuneatus in SEP. CSF protein levels were high (248 mg/dL). We scanned for neuropathy etiologies. We detected a 4-mm nodule in thorax CT only. All infectious, inflammatory, neoplastic and paraneoplastic parameters were normal. He was administered 75 mg pregabalin twice per day for neuropathic pain. In his follow-up examination, motor weakness in the upper limbs, DTR loss, and sensory ataxia were observed. We detected axonal SN in the second EMG. Motor conductions were normal. Needle EMG was normal. There was myelin loss in nerve biopsy. We administered deflazocort 1 mg/kg/d. He progressed in four months so his deflazocort treatment was stopped. During his screening, lung adenocarcinoma was detected (Figure 2). The paraneoplastic auto-antibody test was repeated. Anti-Yo antibody was positive. His motor symptoms progressed and we administered five days of IVIG 0.4 g/kg/day. His sensation symptoms were relieved. We planned 2 g/kg IVIG therapy per month. He underwent surgery and chemotherapy was started. We detected severe axonal SN (there was no sensory response in any sensory nerve) and motor conduction loss in upper limbs in follow-up EMG. In his follow-up, autonomic neuropathy had progressed. First, digestive pseudo-obstruction developed. He then needed mechanical ventilation and we took him our intensive care unit. In spite of the therapy, the patient died.

Paraneoplastic Limbic Encephalitis (PLE)

PLE is characterized by the acute or subacute onset of symptoms that suggest involvement of the limbic system. Patients may develop short-term memory loss or amnesia, become disoriented or may show psychosis including visual or auditory hallucinations or paranoid obsession. Confusion, depression, and anxiety are also common. Generalized or partial complex seizures are seen in about 50% of patients (5,6). The preferentially associated cancers are listed in Table 2.

Case 8

A fifty-six-year-old man was admitted to our clinic with progressive dementia, unusual speech, vertigo, and headache, which he had had for 6 months. There were right-sided focal motor seizures twice in the last 6 months and lung tuberculosis in his medical history. In the neurologic examination, his reaction time was prolonged, he cooperated partially and there was confusion about place and time. There were no meningeal irritation signs or focal neurologic deficits. The Mini Mental Test score was 22/30. We performed cranial magnetic resonance imaging (MRI), which showed prominent hyperintensity in periventricular white matter, thalamus, nucleus lentiformus, bilateral hippocampal and medial temporal lobes in T2 and fluid-attenuated inversion recovery sections with no contrast enhancement (Figure 3). Hydrocephalus

findings were observed in the supra-tentorial compartments. The background rhythm was normal but there were paroxysmal irregular 3-5 Hz slow waves in electroencephalography (EEG) (Figure 4). CSF findings were within the normal range and CSF cultures for mycobacterium tuberculosis were negative. Blood and CSF herpes simplex virus serology were negative. MRI findings, and clinical and laboratory results help diagnose limbic encephalitis. The paraneoplastic autoantibody test was negative. We scanned for neoplasia and found a 4-mm testicular lesion under ultrasonography. We administered 0.4 g/kg/day IVIG for five days but he did not improve significantly. He lost orientation, had confusion, urinary incontinence, and his walking disorder progressed. In his follow-up MRI and EEG, no significant changes were seen. We referred the patient to relevant clinics for his testicular lesion. Later, he developed massive pulmonary emboli and was transferred to the chest diseases hospital.

Case 9

A fifty-four-year-old man was admitted to our clinic with disorientation, episodic amnesia, and right-sided facio-brachial dystonic seizures. There was decreased sodium level in his blood laboratory. We detected a T2-hyper intense area in the left hippocampal area in MRI. His inter ictal EEG was normal. CSF findings were within the normal range. We suspected PLE and we studied paraneoplastic autoantibodies and screened malignancy. We found no antibodies in paraneoplastic screening tests but detected anti-leucine-rich glioma inactivated 1 (anti-LGI1) antibody in autoimmune encephalitis screening tests. We found no malignancy. His symptoms were relieved after IVIG and corticosteroid therapy. He had no PNS. He had typical anti-LGI1 antibody encephalitis clinical condition. His neurological condition was normal in his all control examination.

Discussion

PNS can affect any part of the central and peripheral nervous system, the neuromuscular junction, and muscle. They can be isolated or occur in association (4). In most patients, a neurologic disorder develops before the cancer becomes clinically overt and the patient is referred to a neurologist. Five of our patients' malignancies were diagnosed in our clinic after neurologic symptoms become overt. Even if numerous types of paraneoplastic antibodies (PNA) have been described, less than 50% of patients with PNS have positive results. Thus, the absence of PNA cannot rule out the diagnosis of PNS (4). PNA testing was evaluated in seven of our patients; five of whom were positive for targeting

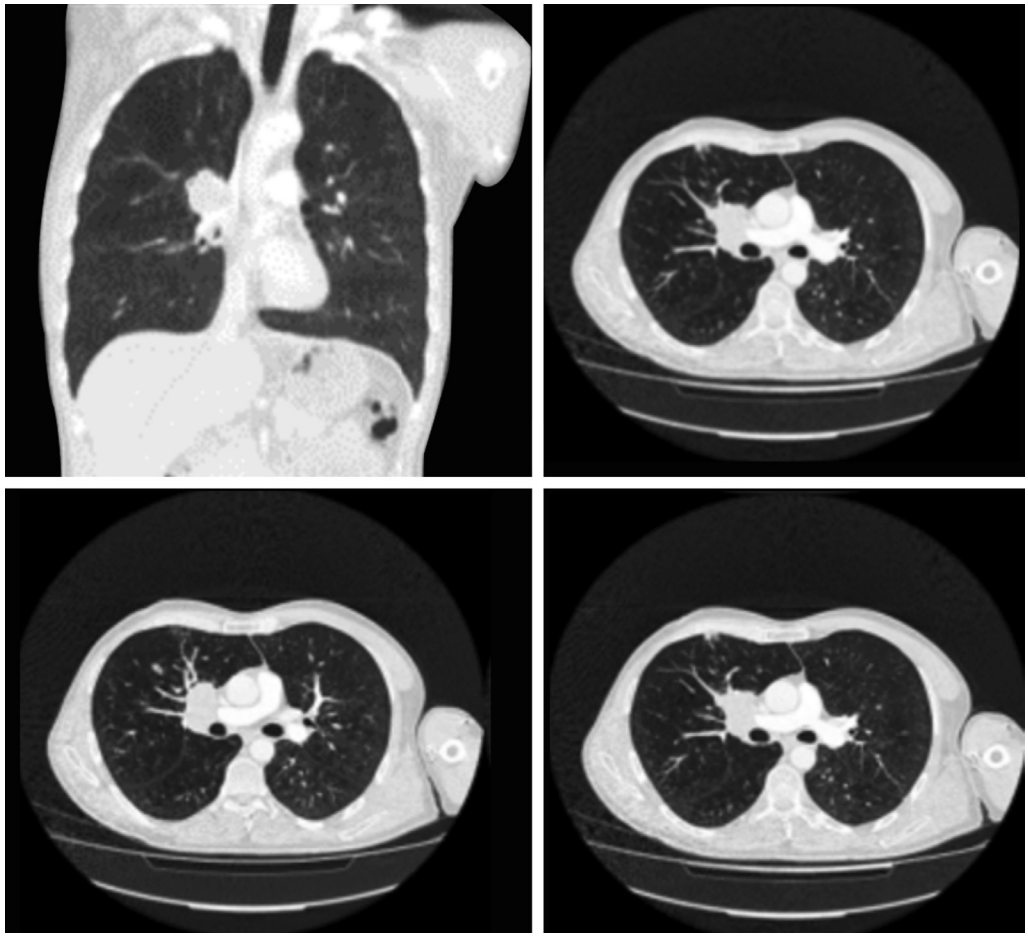


Figure 2. Patient 7, who was diagnosed as having subacute sensory neuropathy associated with lung adenocarcinoma. In the right hilum, a high-density mass lesion 46x27x36 mm was detected, which caused no vascular invasion of neighbouring structures

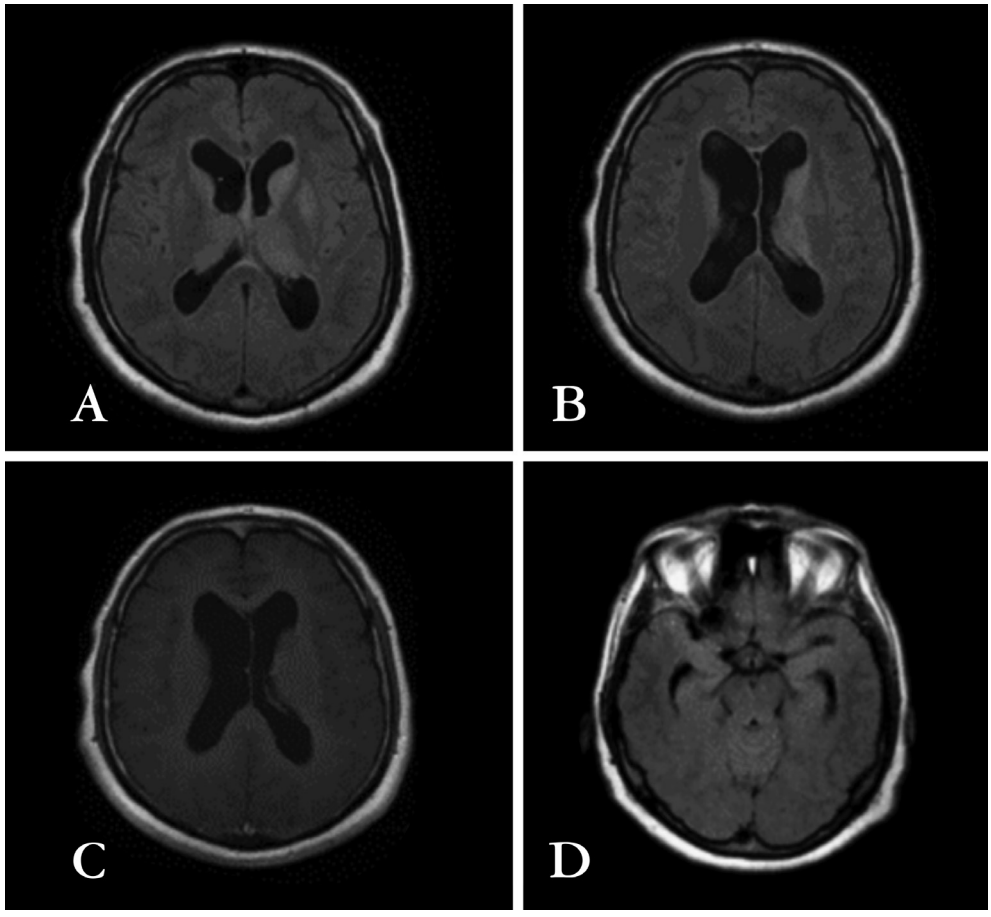


Figure 3. Patient 8, who was diagnosed as having limbic encephalitis. A, B, C) In supra-tentorial slices, there are T2-hyper-intensities in left corona radiate, bilateral thalamus, left lentiform nucleus and bilateral medial temporal areas. D) There was no contrast involvement in post contrast slices.

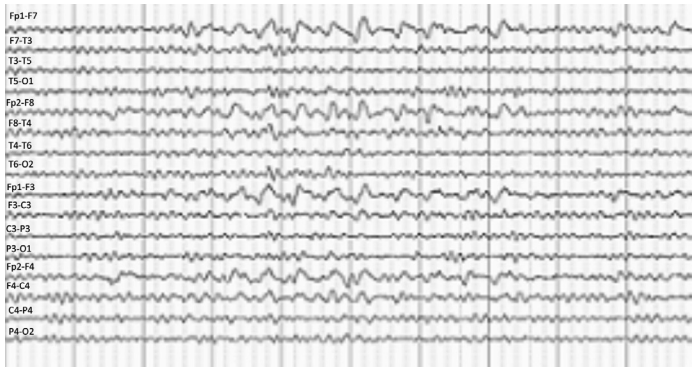


Figure 4. Patient 8, who was diagnosed as having limbic encephalitis. Paroxysmal irregular 3-5 Hz slow waves were observed in electroencephalography

intracellular antigens. One was negative and one was positive to anti-LGI1 antibody, which is against voltage-gated potassium channel (VGKC) complex proteins.

The most frequent entities were SCD and subacute SN (SSN) in the PNS Euronetwork Database (3). The frequencies of other types of PNS are listed in Table 2.

SCD is preferentially associated with ovarian cancer, breast cancer, SCLC or Hodgkin's disease. Yo-Abs are most frequently associated with SCD (3). Our first patient was diagnosed as having breast carcinoma and her PNA was also anti-Yo. Tr-Ab are markers of patients with SCD and Hodgkin's disease, which is the third most common cancer associated with SCD. Unlike Yo-Ab, Tr-Ab usually disappear after treatment of the tumor, or, in a few patients, are only found in CSF (5). Hu-Ab are reported in 23% of patients with SCD and lung cancer. SCD and SCLC are also characteristics for patients with CV2-Ab. Zic4-Ab, Ma2-Ab and VGCC-Ab are present in nearly 40% of patients with SCD and lung cancer (usually SCLC) (3). One of our patients with SCD had been diagnosed as having SCLC and her Hu-Ab was positive. Immune therapy is rarely effective, but there have been reports of an improvement in a few patients after the administration of IVIG, steroids, and plasmapheresis (3). Our patient, whose anti-Hu antibody was positive, was administered IVIG but she had limited benefit. She benefited moderately after steroid treatment.

The detection of GAD-Ab in SPS in almost 70% of patients suggests an autoimmune mechanism. A paraneoplastic variant of SPS has been described in association with breast cancer in women harboring amphiphysin-Ab. SPS has also been reported in association with colon and lung cancer, Hodgkin's disease, and

malignant thymoma (2). The main associated tumor was thyroid carcinoma in one of our patients with SPS. There is no suggestion in the literature of any casual association between SPS and thyroid carcinoma. We scanned the patient every year for new neoplasia but we found no overlapping neoplasia.

Almost 60% of patients with LEMS are paraneoplastic and SCLC is the main associated cancer, detected mostly within two years after the diagnosis of LEMS. No serologic marker for the paraneoplastic etiology exists. VGCC-Ab are present in nearly all patients with LEMS, and these antibodies do not differ between the paraneoplastic and non-paraneoplastic forms (4). Our patient with LEMS was diagnosed as having SCLC in our clinic two months after his symptoms had begun.

SSN is associated with SCLC in 70-80% of cases, but may also occur with breast cancer, ovarian cancer, sarcoma or Hodgkin's disease (2). Most patients with SSN have Hu-Ab, CV2-Ab or amphiphysin-Ab (3). SSN precedes the overt clinical manifestations of cancer with a median delay of 4.5 months (3). Our patient with SSN had anti-Yo and he was diagnosed as having lung adenocarcinoma four months after he was admitted to our clinic. The upper limbs are usually affected first or almost invariably involved with the evolution (3). The involvement of our patient was also upper limbs predominantly. Autonomic neuropathy including digestive pseudo-obstruction is frequent (2,3). In his follow up, digestive pseudo-obstruction developed, his autonomic neuropathy progressed, and he died.

The presence of anti-neuronal ('onconeural') antibodies in a patient with LE raises suspicion for an underlying tumor and can guide the search for the tumor, though some patients with limbic encephalitis have antibodies but no associated tumor. For some patients with paraneoplastic or non-PLE, prompt diagnosis and therapy improve the likelihood of a favorable neurologic outcome (2). Among patients with LE, SCLC is the most commonly associated neoplasm (5). Twenty percent have testicular tumors and 8% have breast cancer (4). One of our patients with LE was detected as having a testicular tumor. The main frequently associated PNA in LE were Hu-Ab, CV2-Ab, Ma2-Ab (2). We found no PNAs in our patients with LE. A recent study evaluated the EEG data of 23 patients with this encephalitis. Seven of them (30.4%) had a unique electrographic pattern, which the authors named 'extreme delta brush' (6). Paroxysmal irregular slow waves activity was recorded in case 8's EEG. "Extreme delta brush" pattern was significantly associated with a more prolonged hospitalization but did not predict a worse outcome (6).

The ninth patient was malignancy free. His symptoms were relieved after IVIG and corticosteroid therapy. His PNA tests were negative. The patient was suspected to have autoimmune encephalitis and his anti-LGI1 autoantibody test was positive. Anti-LGI1 antibodies are against the VGKC complex and are mostly expressed in the hippocampus (7). Hippocampal involvement was also observed in our patient's MRI. Focal seizures can occur in LE but it can be a component of VGKC antibody-associated LE. Faciobrachial localization and hyponatremia can serve as clues for LGI1-associated LE. We would like to emphasize that autoimmune encephalitis is in the differential diagnosis of PNS.

PNS are rare but important entities in clinical practice. The type of auto-antibody and primary cancer are major determinants of the prognosis of diseases. PNS are more common than expected and neurologists should be aware of the variety of the clinical presentations of these syndromes. When physicians suspect PNS, cancer screening should be conducted. Screening must continue even if the results are negative.

Ethics

Informed Consent: Informed consent was taken from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.U.E., S.G., Y.S., Y.B., T.K.İ., H.S.T., Concept: H.U.E., Y.S., Design: H.U.E., Y.S., Data Collection or Processing: H.U.E., S.G., Y.S., Y.B., T.K.İ., H.S.T., Analysis or Interpretation: H.U.E., S.G., Y.S., Y.B., T.K.İ., H.S.T., Literature Search: H.U.E., S.G., Y.S., G.A., Writing: H.U.E., Y.S.

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