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Araştırma Makalesi / Research Article

Analysis of the Patients with Autoimmune Neurological Syndromes in a Single Center in Turkey

Otoimmün Nörolojik Sendromlu Hastaların Türkiye'deki bir Merkezdeki Analizleri

[1]Zeynep Ozozen Ayas, [2]Dılcan Kotan, [3]Emel Oguz Akarsu, [4]Bekır Enes Demıryurek

[1]Eskisehir City Hospital, Department of Neurology, Eskisehir, Turkey
[2]Sakarya University Faculty of Medicine, Department of Neurology, Sakarya, Turkey
[3]Uludag School of Medicine, Uludag University, Department of Neurology, Bursa, Turkey
[4]Bolu İzzet Baysal University, Department of Neurology, Bolu, Turkey

Abstract

Autoimmune neurological syndromes (ANS) are a series of diseases that may involve the central, peripheral, and autonomic nervous system wherein the immune system is affected through varying immunological pathways. In the present study, the clinical and radiological features of the patients diagnosed with ANS were discussed. We reviewed the clinical features, laboratory and radiological findings of 15 patients, who were diagnosed with ANS among those being followed at the hospital. All patients underwent tumor screening tests for paraneoplastic syndrome investigations. Total of 15 patients were included; 11 (73.3%) men and 4 (26.7%) women. The mean age of patients was 50.46±8.49 (32–72) years. Six (40%) patients were diagnosed with paraneoplastic cerebellar degeneration (PCD); three (20%) with limbic encephalitis (LE); two (13.3%) with chronic inflammatory demyelinating polyneuropathy; one (6.67%) with sensorimotor neuropathy; one (6.67%) with motor neuron disease (MND); one (6.67%) with transverse myelitis (TM), one (6.67%) with dermatomyositis. Six (40%) patients had subacute-onset. Chronic symptoms were detected in five (33.3%) patients, acute in four (26.7%) patients. Gait and speech disorders were most common symptoms. The cancer was detected in 10 (three breast, three lung, one liver, one prostate, one thyroid, and one nasopharyngeal cancer) of 15 patients (66.7%). Autoantibody tests revealed GAD-Ab positivity in the patient with LE and anti-Ri, anti-Amphiphysin positivity in the patient with PCD. Seven patients' CSF were analysed. The CSF examination revealed normal findings in three patients with PCD. Pleocytosis was found in patient with TM, while the other three (two LE, one MND) had protein elevation unaccompanied by lymphocytosis. Three of the patients had typical bilateral mesial-temporal involvement in MRI, consistent with LE. Cerebellar atrophy was detected in five of six patients with PCD. ANS span greatly heterogenous neurological disorders. Therefore, a variety of clinical signs and symptoms may be present. Early diagnosis brought about by increased awareness consistently affects treatment. Although the presence of autoantibodies is an important sign, the detection rates are small. Routinely performing cancer screening to facilitate early diagnosis and practicing persistent patient follow-up are the most important factors.

Keywords: Autoimmune neurological syndromes, paraneoplastic cerebellar degeneration, limbic encephalitis, cancer, Turkey

Özet

Otoimmün nörolojik sendromlar (ONS), bağışıklık sisteminin değişik immünolojik yollardan etkilediği santral, periferal ve otonomik sinir sistemini içeren bir dizi hastalıktır. Bu çalışmada ONS tanısı almış hastaların klinik ve radyolojik özellikleri tartışılmıştır. ONS tanısı almış ve hastaneden takip edilmiş 15 hastanın klinik, laboratuvar ve radyolojik özellikleri incelendi. Tüm hastalara, paraneoplastik sendromların araştırılması için tümör tarama testleri yapıldı. Onbiri (%73.3) erkek, 4'ü (%26.7) kadın, toplam 15 hasta dahil edildi. Hastaların ortalama yaşı 50.46±8.49 (32-72) idi. Altı (%40) hastaya paraneoplastik serebellar dejenerasyon (PSD), 3 (%20) limbik ensefalit (LE), 2 (%13.3) kronik inflamatuar demyelizan polinöropati, 1 (%6.67) sensöriomotor nöropati, 1 (%6.67) motor nöron hastalığı (MNH), 1 (%6.67) transvers myelit (TM), 1 (%6.67) dermatomyozit tanısı konuldu. Altı (%40) hasta subakut başlangıçlı idi. Kronik semptomlar 5 (33.3%) hastada, akut 4 (26.7%) hastada saptandı. Yürüme ve konuşma bozuklukları en sık görülen semptomlardı. Kanser 15 hastanın 10'unda (3 meme, 3 akciğer, 1 karaciğer, 1 prostat, 1 tiroid ve 1 nazofarenks kanseri) tespit edildi. Otoantikor testlerinde GAD-Ab pozitifliği LE, anti-Ri ve anti-Amphiphysin pozitifliği PSD'lu hastada saptandı. Yedi hastanın BOS'u analiz edildi. PSD'lu 3 hastanın BOS'u normal bulgular saptandı. TM hastasında pleositoz bulunurken, diğer 3 hastada (2 LE, 1 MNH) lenfositoza eşlik etmeyen protein artışı saptandı. LE'li hastaların üçünde MRG'de tipik bilateral meziotemporal tutulum vardı. PSD'li altı hastanın beşinde serebellar atrofi saptandı. ONS geniş heterojen nörolojik bozukluklara sahiptir. Bu nedenle, çeşitli klinik semptom ve bulgularla ortaya çıkabilmektedir. Artan farkındalığın getirdiği erken tanı, tedaviyi sürekli olarak etkiler. Otoantikorların varlığı önemli bir işaret olmasına rağmen, tespit oranları düşüktür. Erken tanıyı kolaylaştırmak için rutin kanser taraması ve ısrarlı hasta takibi önemli faktörlerdir.

Anahtar Kelimeler: Otoimmün nörolojik hastalık,paraneplastik serebellar dejenerasyon,limbik ensefalit

Correspondence: Zeynep Ozozen AYAS- Department of Neurology, Eskişehir City Hospital, Eskişehir, Turkey.
e-mail:zozozen@hotmail.com
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1. Introduction

Autoimmune neurological syndromes are a series of diseases that may involve the central, peripheral, and autonomic nervous system wherein the immune system is affected through varying immunological pathways. It is thought that tumor antigens initiate immune-mediated processes in paraneoplastic autoimmune neurological disorders. In autoimmune neurological disorder, which typically manifests with a subacute course, neurological symptoms are seen before the underlying tumor appear in 65% of patients (1). The intracellular antigen-target B-cell response reveals the association between the malignancy and the autoimmune neurological syndrome (2). The presence of autoantibodies in tissues also suggests autoimmunity which is in the disease etiology. However, these antibodies cannot be detected in 20 to 50% of patients (3).

In the present study, the clinical and radiological features of 15 patients diagnosed with autoimmune neurological syndromes were discussed. After the diagnosis both features allowed for the detection of different cancer types and increased treatment opportunities.

2. Material and Methods

We reviewed the clinical features, laboratory and radiological findings of 15 patients, who were diagnosed with autoimmune neurological syndrome among those being followed at the Neurology Clinic of Sakarya University Training and Research Hospital between 2016 and 2019. Encephalitis and infectious diseases were excluded. Age, sex, premorbid disorders, admission symptoms, cerebrospinal fluid (CSF) results (glucose/simultaneous blood glucose, protein, sodium, chloride, cultures, HSV PCR), autoantibodies (anti-Hu, anti-Yo, anti-Ri, anti-CV2, anti-Ma, anti-Amphiphysin, anti-NMDA-R, anti-AMPA-1, anti-AMPA-2, anti-CASPR-2, anti-LGI-1, anti-GABAR B1, glutamic acid decarboxylase antibody (GAD-Ab)), magnetic resonance imaging (MRI), electroneuromyography (ENMG) results, cancer screening (tumor marker tests, thoracic and abdominal computed tomography (CT), thyroid ultrasonography (USG) mammography and pap smear tests for women, prostate USG for men, fluoro-D-glucose positron emission tomography (FDG-PET)), treatment protocols, and survival data were assessed. The study complies with the Helsinki Declaration, and approval was obtained from the ethics committee of Sakarya University.

3. Results

In this study, the files of 2964 patients who hospitalized in a neurology clinic were retrospectively examined. A total of 15 patients (11 (73.3%) men and 4 (26.7%) women) who were diagnosed with autoimmune neurological syndrome were included in our study. (Table 1) The mean age of patients was 50.46±8.49 (32–72) years. Six (40%) patients were diagnosed with paraneoplastic cerebellar degeneration (PCD); three (20%) with limbic encephalitis (LE); two (13.3%) with chronic inflammatory demyelinating polyneuropathy (CIDP); one (6.67%) with sensorimotor neuropathy; one (6.67%) with motor neuron disease; one (6.67%) with transverse myelitis, one (6.67%) with dermatomyositis. (Table 1)

Table 1. Gender of patients and autoimmune neurological syndromes types.

	#	Percentage
Gender		
Male	11	73.3
Female	4	26.7
Types		
PCD	6	40
LE	3	20
CIDP	2	13.30
SMN	1	6.67
MND	1	6.67
TM	1	6.67
DM	1	6.67

PCD: Paraneoplastic cerebellar degeneration; LE: Limbic encephalitis; CIDP: Chronic inflammatory demyelinating polyneuropathy; SMN: Sensorimotor neuropathy; MND: Motor neuron disease; TM: Transverse myelitis; DM: Dermatomyositis.

Seven (46.6%) patients had gait disorder, two of them had speech disorder, one behavioral disorder, additionally. Five (33.3%) patients presented with symptoms of limb weakness. One of them had coexisting speech disturbance, two had hyperesthesia. A patient with sensoriomotor neuropathy had weakness of upper extremity and pain which is a rare symptom of autoimmune neurological syndrome. Five (33.3%) patients had impaired speech, and one of five had limb weakness and two had gait disturbance as symptoms. Only one (6.6%) patient in our study cohort had seizure and impaired consciousness as an initial symptom of LE. (Table 2) Symptoms were divided into three groups; acute, defined as less than four weeks; subacute, lasting four to twentyfour weeks; and chronic, lasting more than twentyfour weeks. Six (40%) patients had subacute symptoms. Chronic symptoms were detected in five (33.3%) patients, acute in four (26.7) patients. (Table 2)

Nine (60%) patients had no history of systemic disease. Two patients had hypertension. The patient with PCD had diabetes mellitus and hypothyroidism. Another patient with PCD had breast cancer; the patient with LE had Behçet's disease, the patients with sensorimotor neuropathy had DM. (Table 2)

Table 2. Detailed clinical features of the patients with autoimmune neurological syndromes.

	Age	Gender	Diagnosis	Symptoms	The duration of the ymptoms	Premorbid Disease
1	44	M	PCD	weakness of limb, speech disorder	Subacute	Diabetes mellitus, hypothyroidism
2	47	F	PCD	speech and gait disorder	Subacute	Breast cancer
3	56	M	PCD	gait disorder	Chronic	-
4	46	M	PCD	gait disorder	Chronic	-
5	44	M	PCD	speech disorder	Subacute	Hypertension
6	62	M	PCD	speech and gait disorder	Chronic	-
7	60	M	LE	speech disorder	Subacute	-
8	38	F	LE	seizure	Acute	-
9	36	M	LE	behavioral and gait disorder	Acute	Behçet's Disease
10	70	M	CIDP	weakness and parestesia of extremities	Subacute	Hypertension
11	48	F	CIDP	weakness and parestesia of lower extremities	Chronic	-
12	62	M	SMN	weakness and pain of right arm	Acute	Diabetes mellitus
13	72	M	MND	weakness of left lower extremity	Subacute	-
14	40	F	TM	gait disorder	Acute	-
15	32	M	DM	Gait disorder	Chronic	-

PCD: Paraneoplastic cerebellar degeneration; LE: Limbic encephalitis; CIDP: Chronic inflammatory demyelinating polyneuropathy; SMN: Sensorimotor neuropathy; MND: Motor neuron disease; TM: Transverse myelitis; DM: Dermatomyositis

All patients underwent tumor screening tests for paraneoplastic syndrome investigations. The cancer was associated with autoimmune neurological syndromes in 10 (three breast, three lung, one liver, one prostate, one thyroid, and one nasopharyngeal cancer) of 15 patients (66.7%). Four of six patients with PCD were diagnosed with different types of cancers. (breast, lung, thyroid and nasopharyngeal cancer) Tumor was not detected in three patients with LE. The symptoms of autoimmune neurological syndromes appeared before the diagnosis of cancer, except one patient. The patient with PCD had diagnosis of breast cancer before symptoms of PCD. (Table 3)

Table 3. The findings of CSF, neuroimaging, tumor screening test and theraphy of the patients with autoimmune neurological syndromes.

	Diagnosis	CSF Sings	Antibody	Neuroimaging/test	Neoplasia	Theraphy
1	PCD	Normal	Negative	MRI	Negative	IVIG
2	PCD	NA	NA	MRI	Breast cancer	-
3	PCD	Normal	Anti-Ri, Anti-Amphiphysin	MRI	Lung cancer	IVIG
4	PCD	Normal	Negative	MRI	Thyroid cancer	IVIG
5	PCD	NA	NA	MRI	Nasophargeal cancer	IVIG
6	PCD	NA	NA	MRI	Negative	IVIG
7	LE	Elevated protein	Negative	MRI	Negative	IVIG
8	LE	Elevated protein	Anti-GAD	MRI	Negative	IVIG
9	LE	NA	Negative	MRI	Negative	IVIG + MP
10	CIDP	NA	NA	MRI-ENMG	Prostat cancer	IVIG + MP
11	CIDP	NA	NA	MRI-ENMG	Breast cancer	IVIG
12	SMN	NA	NA	MRI-ENMG	Lung cancer	IVIG
13	MND	Elevated protein	Negative	MRI-ENMG	Lung cancer	IVIG
14	TM	Pleocytosis	Negative	MRI	Breast cancer	IVIG + MP
15	DM	NA	NA	MRI-ENMG	Liver cancer	IVIG + MP

PCD: Paraneoplastic cerebellar degeneration; LE: Limbic encephalitis; CIDP: Chronic inflammatory demyelinating polyneuropathy; SMN: Sensorimotor neuropathy; MND: Motor neuron disease; TM: Transverse myelitis; DM: Dermatomyositis; NA: Not avaliable; CSF: Cerebrospinal fluid; MRI: Magnetic resonance imaging; ENMG: Electroneuromyography (ENMG); IVIG: Intravenous immunoglobulin; MP: Methylprednisolone

The patient with CIDP had elevated carcinoembryonic antigen (CEA) in tumor screening tests and he was diagnosed with prostate adeno carcinoma by FDG-PET. The patient with sensorimotor neuropathy was diagnosed with small cell lung cancer that developed five and a half years later. The patient with PCD was diagnosed with bronchoalveolar cancer; another patient with PCD was diagnosed with thyroid papillary carcinoma, the patient with transverse myelitis was diagnosed with invasive ductal breast cancer; the patient with dermatomyositis had hepatocellular carcinoma. No malignancy was detected in 5 (33.3%) patients during the follow-up period. Autoantibody tests revealed GAD-Ab positivity in the patient with LE and anti-Ri, anti-Amphiphysin positivity in the patient with PCD. (Table 3)

Seven patients' CSF were performed. The CSF examination revealed normal findings in three patients with PCD. Pleocytosis was found in patient with transverse myelitis, while the other three (two LE, one motor neuron disease) had protein elevation unaccompanied by lymphocytosis. All patients had a negative CSF culture and HSV PCR. (Table 3)

All 15 patients underwent brain/spinal MRI studies. Three of the patients had typical bilateral mesial-temporal involvement in FLAIR and T2 sequences, consistent with LE. Cerebellar atrophy was detected in five of six patients with PCD. The patients diagnosed with CIDP, sensorimotor neuropathy, dermatomyositis and motor neuron disorders were diagnosed with ENMG. CIPD was characterized by conduction blocks, reduced composite muscular action potential (CMAP) responses, and neurogenic motor unit potential changes. The ENMG examination of the patient with motor neuron disease showed reduced motor CMAP responses in all extremities, diffuse denervation and fasciculation at rest, and motor unit potential loss at maximal contraction. (Table 3)

Fourteen patients were treated with 0.4 mg/kg intravenous immunoglobulin (IVIG) for five days followed by IVIG maintenance therapy. Four of twelve patients who had no or limited benefit from IVIG, had methylprednisolone therapy for seven days. The patient with breast cancer who was diagnosed PCD had not allow any treatment. The patients diagnosed with lung cancer, invasive ductal breast, liver, prostate cancer, thyroid papillary and nasopharyngeal carcinoma, underwent surgical excision and oncological treatment. (Table 3)

4. Discussion

Immune system response is multifactorial, complex, and individualized (4). Different autoreactive processes have been defined. However, no clear etiological factor could be found in 50% of autoimmune disorders. It is important to assess different pathophysiological processes, predict different clinical spectrum, and develop early therapeutic approaches to such disorders. The certain incidence of the disease is unknown, it was determined as 0.51% in our study. We suggest that assessing patients presenting with a variety of clinical spectrums will contribute to the existing literature. PCD is a rare, severe neuroimmunological disorder that may accompany tumors. Gender factor is not certain in PCD. Fu et al. reported seven patients with PCD who were female (5). Among 28 patients with PCD 22 were male in another study.

6 Male dominance is remarkable in our study. (5/6) PCD's clinical features can be variable. Common symptoms are moderate to severe truncal ataxia, nystagmus, vertigo, dysarthria, and diplopia. Gait and speech disorders were most common symptoms in our six patients with PCD. Acute or subacute onset can be seen. But in our study, subacute and chronic onsets were detected. PCD is frequently associated with gynecological tumors, lung cancer, and Hodgkin's lymphoma (7,8,9). Breast, thyroid, lung and nasopharyngeal cancers were detected in four of six patients with PCD in our study. Autopsy findings include reduced cerebellar size and the diffuse loss of Purkinje cells, granules, and basket cells in the cerebellar cortex. A difficulty with PCD diagnosis is that most reported PCD cases have a normal radiography and that many cases appear well before cancer is diagnosed (10). Indeed, radiological changes in cerebellar size usually appear only in the late stage of the disease (11). On the other hand, Scheid et al. reported cerebellar atrophy occurring within 1 month of symptom onset (12). In our study, three patients had subacute, three had chronic symptoms. And five of six patients with PCD had cerebellar atrophy in MRI. PCD patients mostly have anti-Yo or anti-Ri associated onconeural antibodies. In rare antibody negative PCD cases, the neurological disease rapidly progresses and appears to be non-treatable (13). Three CSF antibody studies could not be done as no permission could be obtained from that patients, in our study. Anti-Ri associated PCD mainly presents opsoclonus-myoclonus-ataxia. Bronchoalveolar cancer was detected in a 56-year-old man patient who was presented with ataxia and cerebellar signs. The patient had anti-Ri and anti-Amphiphysin antibodies. Anti-Ri and anti-Amphiphysin are well-characterized onconeural antibodies. Anti-Ri is commonly associated with breast, gynecological and small cell lung cancer; anti-Amphiphysin is associated breast, overian, and lung cancer. A 46-year-old man, who had progressive gait disorder and cerebellar atrophy on MRI, was diagnosed with PCD. Thyroid papillary carcinoma was detected with malignancy screening. The association of PCD and thyroid cancer is extremely rare and has been reported in only two patients in the literature (14,15). A 44-year-old man who had PCD, diagnosed with nasopharyngeal carcinoma with tumor screening tests.

PCD has a poor prognosis and treatment options are limited. IVIG, corticosteroids, plasmapheresis, and cyclophosphamide have been tried alone or in combination and have yielded partial response rates. It has been reported that the resection of the primary tumor decreases PCD's neurological symptoms (16,17). The median survival time of patients treated with anti-tumor therapy has been reported to be longer than that of untreated patients (18). In our study, the patient with breast cancer refused any therapy. Three patients benefited partially from the IVIG therapy. Two patients had no response to IVIG.

LE forms a group of autoimmune disorders that is increasingly diagnosed with heightened awareness. An external factor like a tumor or infection triggers lymphocyte production. This is followed by a disturbed blood brain barrier, allowing immune cells to enter the central nervous system. B lymphocytes cause the disease with lymphocytes proliferating in the central nervous system, transforming into plasma cells, and producing intrathecal antibodies. Seizures, memory loss, depression, and cognitive impairment are its characteristics (19). The symptoms occur as acute or subacute. Similarly, two patients had ac ute, one patient had subacute onset, in our study. In addition to the clinical signs and symptoms, hyperintensity in the temporal regions in FLAIR MRI and an autoantibody presence in the CSF have increased the diagnosis rates. Three of the 15 patients were diagnosed with LE clinically and radiologically, in our study.

One patient presented with seizure and confusion, another with altered behavior and gait disorder, and another with speech disturbance. Typical MRI findings were seen in acute period of all patients. In the literature, a patient was reported with MRI findings appearing 26 days after the onset of symptoms, despite the normal initial MRI examination (20). A 36-year-old man who was diagnosed with Behçet's disease for 9 years had altered behavior. Neurological involvement occurs at a mean of five years after the onset of this disease. It commonly manifests as parenchymal central nervous system involvement and dural sinus thrombosis (21). This case is worth noting because it is a rare example of Behçet's disease with neurological involvement occurring with LE. A 38-year-old woman with LE that presented with seizure and confusion had pleocytosis and elevated protein in the CSF examination. The patient with negative CSF autoantibodies had serum GAD-Ab positivity. A study reported the presence of GAD-Ab at a rate of 17.5% (22). A co-existing malignancy was detected in a limited number of LE patients with GAD-Ab positivity (22,23). Our patient with GAD-Ab positivity was not found to have any malignancy in the two years follow-up tumor screening. Data in the literature suggest that GAD-Ab positive patients respond favorably to immunotherapy (22,24,25).

Similarly, this case responded dramatically to IVIG. The autoantibody tests of the other two LE patients were negative and the patient with Behçet's disease responded to IVIG and MP, while the other patient responded to IVIG. The most common malignancies associated with paraneoplastic LE are small cell lung cancer, testis tumors, breast cancer, teratoma, and Hodgkin's lymphoma (26). In two-thirds of cases, a malignancy can be diagnosed three to five months after the emergence of neurological signs. However, screening should be done for five years at follow-up. No malignancy could be diagnosed during the three-year follow-up of the three patients with LE, in our study.

CIDP is a proximal and distal demyelinating peripheral neuropathy with a slow course or exacerbations, which causes symmetrical motor involvement rather than sensory involvement (27). Its co-occurrence with diabetes mellitus, systemic lupus erythematosus, and lymphoproliferative disorders is known. A similar association was also reported with non-Hodgkin's lymphoma, hepatocellular carcinoma, and osteosclerotic myeloma (28,29,30). Studies have reported the co-occurrence of CIDP with breast and prostate cancers, which were rarer in our cases. In one of our cases, an elevated CEA level and prostate cancer on the PET were diagnosed in the cancer screening. However, that patient refused surgery, so IVIG and MP treatment were started, which yielded a partial response.

Paraneoplastic neuropathy is a form of autoimmune neurological syndromes. The most common initial signs of paraneoplastic neuropathy are sensory loss (67.4%), pain (41.3%), weakness (22.8%), and sensory ataxia (20.7%). In a study where 92 patients were enrolled, pain was the initial symptom in 13% of the patients (31). Multiple symptoms were present in 39.1% of the study population. Our case also had pain and weakness. It was shown in the literature that 57.6% of patients presented with pain secondary to neuropathy in the course of painful peripheral neuropathies. The most common disorder was sensorineural ganglionopathy (25%), followed by symmetrical sensorimotor (22.8%), symmetrical sensory (22.8%), mononeuritis multiplex (6.5%), pure motor (7.6%), and demyelinating (12%) injury. Hematologic (16.3%) and gastrointestinal system (12%) malignancies are seen (31). Our case was diagnosed with small cell lung cancer five and a half years later. Clinicians should be aware that there may be an underlying malignancy in painful peripheral neuropathies.

Paraneoplastic motor neuron disease is so rare. Diagnosis is very important because it is treatable. Although the disease's clear diagnostic criteria are still uncertain, its main features have been determined in the latest studies (32). Subacute, lower motor neuron syndrome, asymmetrical upper extremity involvement, the presence of signs of inflammation in the CSF, and treatment with immunotherapy or anti-tumor therapy are the main features. Our case presented with motor neuron disease characterized by subacute lower extremity involvement, suggesting a paraneoplastic syndrome.

Dermatomyositis is an inflammatory myopathy characterized by progressive symmetrical proximal muscle weakness and skin signs. Its etiology is unclear. Patients with dermatomyositis face a high risk of developing an accompanying malignancy (6–60%) (33). The most common malignancies are ovarian, lung, breast, stomach, and colorectal cancer. Age, diffuse and severe skin involvement, severe muscle weakness, and serum creatine kinase elevation increase the risk of cancer. In our study, a young male patient presented with proximal motor weakness with subacute onset.

5. Conclusion

Although many antibodies have been defined in recent years, less than 50% of patients have positive results, thus the absence of these antibodies does not exclude the possibility of neurological syndromes (34). As some patients did not consent to an antibody screen of the CSF, it could not be performed; only a patient with LE had GAD-Ab positivity and a patient with PCD had anti-Ri and anti-Amphiphysin antibodies. The presence of two antibodies is a rare combination.

Autoimmune neurological syndromes span greatly heterogenous neurological disorders. Therefore, a variety of clinical signs and symptoms may be present. Early diagnosis brought about by increased awareness consistently affects treatment. Although the presence of autoantibodies is an important sign, the detection rates are small. Routinely performing cancer screening to facilitate early diagnosis and practicing persistent patient follow-up are the most important factors.

Authors' contributions ZÖA, DK, ED and EOA contributed to the study design and concept. ZÖA, DK, ED and EOA contributed to analysis and interpretation of data. ZÖA and DK were responsible for primary data analysis. AT, AKT, BDG and EA contributed to the writing and review. All authors read and approved the final manuscript.

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