Sarcoidosis is an inflammatory, multisystemic disease that can affect many organs, such as the lungs, lymph nodes, skin, and eyes. Nervous system involvement is observed in 5%-15% cases; in 70% cases, neurological symptoms occur within the first 2 years of the systemic disease onset (1). Central nervous system (CNS) involvement of sarcoidosis may affect the cranial nerves (52%), particularly the facial nerve, meninges, brain parenchyma, and hypothalamus. Various symptoms, such as encephalopathy, seizures, myelopathy, meningeal syndrome, and cerebellar involvement, may be presented (2). Diagnosis remains difficulties as there are no specific clinical and/or radiological symptoms of neurosarcoidosis (NS), mainly in patients without systemic manifestations. Diagnosis can be accurate by detecting histopathological non-caseified granulomas associated with clinical and radiological symptoms. Clinical follow-up and treatment modalities for neurosarcoidosis remain unclear because the disease is rare; early treatment is reported as important in terms of mortality and morbidity. In treatment, while corticosteroids are the first line, immunosuppressive treatments can be applied in refractory cases.

In this context, we aimed to discuss the radiological and/or histopathological characteristics and treatment modalities in 7 cases of NS as a result of detailed investigations.

CASES
Table 1 demonstrates the clinical and radiological characteristics of the patients with NS who were referred to our institution between 2006 and 2013.

Case 1: An 18-year-old male patient, with an unremarkable medical history, was admitted to in November 2010 with complaints of sudden onset of weakness in right arm and leg, blurred vision of right eye and dysarthria. A gadolinium-enhancing lesion at the right optic tract was detected in cranial MRI. Neoplastic, metabolic, and inflammatory diseases were evaluated for the etiology; however, no pathology was detected; and his complaints spontaneously resolved within 2 months.

Further, a second attack with right-sided weakness and dysarthria occurred in April 2011, and cranial MRI revealed gadolinium-enhanced lesions in mesencephalon and pons in addition to the optic tract. A mild protein increase in (48 mg/dL) cerebrospinal fluid (CSF) examination was also detected. Oligoclonal band (OCB) was found negative. He was diagnosed with sarcoidosis as a result of a liver biopsy performed because of lymphadenomegaly discerned in the liver during systemic screening. One month later (May 2011), upon acute clinical right facial paralysis, diplopia, difficulty in walking and progression of lesions in radiological images, he was administered 60 mg/day oral steroid and 6 months methotrexate (MTX) in another center. Clinical and radiological progression was detected...
A 17-year-old male patient was referred to our clinic in June any complaint. He is still being followed up without decreased to 10 mg/day), and anti-epileptics (carbamazepine 900 mg/day; levitiracetam 500 mg/day). There was a significant decrease observed in seizure frequency and duration with the treatment of azathioprine (150 mg/day), oral steroid and continued with 1 mg/kg/day oral steroid and antiepileptic drug therapy.

Case 2: A 17-year-old male patient was referred to our clinic in June 2011 because of recurrent generalized seizures over the course of a few days. EEG examination revealed diffuse bioelectrical disorganization and cranial MRI revealed gadolinium enhanced lesions at the left frontal and cerebellar regions (Figure 2). CSF evaluation was unremarkable. Bilateral hilar lymphadenopathy (LAP) was detected in the thorax CT, performed for differential diagnosis. She had no previous systemic complaint, and sarcoidosis was diagnosed performing the thorax biopsy. Cerebral involvement was evaluated as NS, and she was treated with an oral steroid (1 mg/kg/day) and antiepileptic (levetiracetam 1500 mg/day), following intravenous methylprednisolone (IVMP) treatment (1 g/day) for 7 days. In her last follow-up examination, the frequency of the seizures remarkably reduced, and a prominent regression of lesions was observed in radiological images.

Case 3: A 39-year-old female patient, without any remarkable medical history, was admitted to our outpatient clinic on December 2006 because of recurrent generalized seizures over the course of a few days. EEG examination revealed diffuse bioelectrical disorganization and cranial MRI revealed gadolinium enhanced lesions at the left frontal and cerebellar regions (Figure 2). CSF evaluation was unremarkable. Bilateral hilar lymphadenopathy (LAP) was detected in the thorax CT, performed for differential diagnosis. She had no previous systemic complaint, and sarcoidosis was diagnosed performing the thorax biopsy. Cerebral involvement was evaluated as NS, and she was treated with an oral steroid (1 mg/kg/day) and antiepileptic (levetiracetam 1500 mg/day), following intravenous methylprednisolone (IVMP) treatment (1 g/day) for 7 days. In her last follow-up examination, the frequency of the seizures remarkably reduced, and a prominent regression of lesions was observed in radiological images.

Case 4: A 16-year-old male patient was admitted to our clinic in November 2012 with a complaint of diplopia after an upper respiratory tract infection. He mentioned that 3 years ago, he was evaluated by another clinic because of an acute onset of bilateral blurred vision and paraparesis. On neurological examination, papilloedema was detected, and cranial and spinal MRIs and CSF examinations were performed. OCB was negative, and there was mild leukocytosis and increased protein in CSF. There was no other pathology in the serum other than Varicella zoster IGM positivity. Complaints spontaneously ceased within 2 months. His previous medical history and family history were unremarkable, and upon examination in our clinic, there were no symptoms except a limitation in right eye abduction. Nodular-type pial infiltration at supra-infra tentorial...
was performed after the diagnosis of NS. The patient’s clinical complaints detected high (11.1 U/L). High dose 7 days IVMP treatment (1 gr/day) was confirmed by biopsy. In CSF glucose was low (20 mg/dL), protein (49.2 mg/dL), IgG index 0.93 (>0.7), ACE was 10 U/L (>2.5 U/L), and OCB pattern was 4 positive and ACE level was normal, excluding high serum angiotensin-converting enzyme (ACE) levels. Serum and CSF ACE levels were 98 U/L and 5.3 U/L, CSF protein levels were high (93.6 mg/dL), and oligoclonal band (OCB) was negative. The patient was diagnosed with NS and was administered a high dose (1000 mg/day) intravenous methylprednisolone (IVMP) treatment for 7 days. Complaints resolved on the 3rd day of treatment, and the patient was prescribed oral steroids for long-term treatment.

Case 7: A 55 year-old male patient presented with sudden onset right arm and leg weakness, imbalance, and dysarthria on August 2011. Upon neurological examination of the patient, who was previously diagnosed with sarcoidosis and had used intermittent oral steroid treatment since 2005, dysarthria and ataxia were the prominent clinical features. Cranial MRI revealed gadolinium enhanced lesions on the left side of thalamus and pons extended from the right brachium ponti to right cerebellum compatible with NS (Figure 2). In CSF examination, protein increased (49.2 mg/dL), IgG index 0.93 (>0.7), ACE was 10 U/L (>2.5 U/L), and OCB was pattern 3 positive; no pathological cells were detected. The case was diagnosed as NS as the result of serum ACE level 77 U/L (8-52 U/L) and protein (70 mg/dL) levels in CSF examination, the patient was diagnosed with NS and was administered a high dose IVMP for 7 days after switching to prophylactic oral steroid treatment. Regression of clinical findings and MRI lesions were improved on the 7th day of treatment, and prominent regression was detected in control radiological images after 3 months.

DISCUSSION

Nervous system involvement is observed in 5%-15% cases of systemic sarcoidosis, and in 70% cases, neurological involvement occurs within 2 years after diagnosis of sarcoidosis diagnosis (1,2). Sarcoidosis may affect cranial nerves (52%), particularly the facial nerve. Meningeal, parenchymal, and hypothalamic lesions were also observed in CNS involvement of sarcoidosis.

Sarcoidosis can present with variable symptoms, such as encephalopathy, seizure, myelopathy, meningeal syndrome, and cerebellar signs. NS cases have exhibited 56.6% cranial neuropathy, 33.3% epileptic seizures, 16.6% peripheral nerve system symptoms comprising neuropathy/myelopathy (1,3,4,5). Bell’s paralysis because of facial nerve and optic nerve involvement are the most common cranial neuropathies ob-
in a histopathological evaluation. In 5 cases, diagnosis was accurate by detecting non-caseified granulomas. In neurological examination of the brain, meninx, pulmonary, or conjunctiva biopsies, diagnosis; however, NS can be accurately diagnosed with histopathological detection of non-caseified granulomas that accompany clinical and radiological features (18,19). Magnetic resonance imaging (MRI) is the most sensitive imaging method (82%-97%) in NS diagnosis. Although various intracranial and spinal lesions, such as leptomeningeal involvement and white matter lesions, can be detected, these findings are nonspecific for sarcoidosis, para/tetra paresis, autonomic dysreflexia, radicular syndrome, or cauda equine syndrome can be observed because of transverse myelopathy (11,12,13,14,15).

In 2 cases followed in our clinic, sarcoidosis had been previously diagnosis, and all cases were admitted with various neurological symptoms, such as epileptic seizures, cranial neuropathy, diplopia, dysarthria, trigeminal neuralgia, and hemiparesis. Diagnosis of NS remains challenging, particularly in cases that present with only neurological symptoms, without a previous diagnosis of sarcoidosis (16,17). Cases can be diagnosed by histopathological detection of non-caseified granulomas that accompany clinical and radiological features (18,19). Magnetic resonance imaging (MRI) is the most sensitive imaging method (82%-97%) in NS diagnosis. Although various intracranial and spinal lesions, such as leptomeningeal involvement and white matter lesions, can be detected, these findings are nonspecific for NS diagnosis and not correlated with its clinical symptoms (20).

CSF is a diagnostic method in NS cases. Along with the detection of non-specific findings, such as protein increase, the levels of leukocytosis or pleocytosis, ACE (21,22), immune globulin G index, CD4:CD8 lymphocyte ratio (23), an increase of beta 2-microglobulin, and the positivity of oligoclonal band (OCB) in CSF provides important clues for NS diagnosis. However, CSF examination can be normal in NS cases (5,18,24). In 6 of our cases, an increment in protein and ACE levels was detected in CSF examinations; pattern III OCB positivity in one case and pattern IV OCB positivity in one case were observed. Similar CSF findings may be present in multiple sclerosis, systemic lupus erythematosus, CNS infections, and tumors. Although it is not a specific diagnostic method, high serum ACE is detected in 86.3% of NS cases. All these examinations may support diagnosis; however, NS can be accurately diagnosed with histopathological examination of the brain, meninx, pulmonary, or conjunctiva biopsies (1,2). Of the 7 cases we have presented clinically, 5 began with clinical neurological symptoms, and there were no systemic sarcoidosis findings. In 5 cases, diagnosis was accurate by detecting non-caseified granulomas in a histopathological evaluation.

As the disease is rarely observed, data including clinical follow-up and treatment in NS progressing with CNS involvement is insufficient (25). In all, 2/3 cases positively responded to treatment, and prognosis is slower and stationary in treated cases (26). In the study conducted by Ferriby et al, it has been emphasized that early treatment in NS is important for prognosis as CNS involvement is considered to have a poor prognosis (27). Furthermore, Allen et al have reported that 84% of the treated cases and 38% of the non-treated ones have neurologically recovered, and the best response to treatment has been obtained in peripheral nervous system involvement (28). NS has poorer diagnosis in young cases and cases where CNS involvement occurs in the early stages (1).

Corticosteroids are the first choice in neurosarcoidosis treatment (Table 2). Rather than other system involvement, including pulmonary involvement, treatment doses should be higher in CNS involvement (29). Usually, treatment is initiated with 1 mg/kg/dose prednisolone and is expected to continue for 6-8 months (24,30). Because of the side effects of long-term high dose oral steroid treatment, use of low-dose oral steroid together with intermittent high-dose intravenous bolus treatment is recommended. Moreover, in 2/3 of the cases with steroid treatment, clinical and radiological improvement can be maintained. Immune suppressive treatments, such as azathioprine, methotrexate (MTX), cyclosporine, or cyclophosphamide, are used in patients who do not respond to steroid treatment (31). It is reported that clinical response can be maintained at 60% with MTX treatment and 75% with cyclophosphamide treatment (32,33,34). Treatments, such as infliksimab and mycophenolate mofetil, should be considered in immunosuppressive-resistant cases (24,25,30). In our cases, treatments were arranged as 1 g dose of intravenous corticosteroid for 5-7 days and oral steroid continued by tapering. Cyclophosphamide and/or methotrexate treatments were prescribed in patients without clinical or radiological improvement. Clinical and radiological progression was observed in only one case, while under cyclophosphamide treatment, in other cases, partial benefit was observed.

Sarcoidosis can progress with different clinical symptomatology and radiological symptoms. Diagnosis of NS is very difficult, particularly when the initial symptoms presented with neurological involvement. Infections, such as tuberculosis, neurosyphilis, toxoplasmosis, Behçet Syndrome, lymphoma, meningeal carcinomatosis, other malignancies, and demyelinating diseases, should be considered for differential diagnosis, and detailed ex-

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Initial dose</th>
<th>Side effects</th>
<th>Explanations</th>
</tr>
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<tbody>
<tr>
<td>Prednisone</td>
<td>1 mg/kg/day, po</td>
<td>Osteoporosis, Cushing syndrome, hypertension, diabetes, peptic ulcer, pseudotumor cerebri, glomer, cataract, euphoria, psychosis</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>1000 mg/day I.V 3 days</td>
<td>Very rare for 3 days treatment</td>
<td>Should be used combined with folic acid (1 mg day po)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10-25 mg once a week: po or sc</td>
<td>Anemia, neutropenia, hepatic dysfunction, pneumonia</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>5 mg/day should be given in two different doses</td>
<td>Renal failure, hypertension</td>
<td>Expensive</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50 mg, po</td>
<td>Anemia, neutropenia, hepatic dysfunction</td>
<td>Cheap</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>50-200 mg po or once in 2-3 weeks 500 mg IV</td>
<td>Cystitis, neutropenia</td>
<td>Urinary function follow up in terms of microscopic hematuria</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200 mg/day po</td>
<td>Retinopathy, auto toxicity, myopathy, cardiomyopathy, neuropathy, neurophysiologic effect</td>
<td>Routine eye examination with 3-6 months intervals</td>
</tr>
<tr>
<td>Infliksimab</td>
<td>3 mg/kg I.V 1,3,5.weeks: then once in each 6 weeks</td>
<td>Fever, headache, dizziness, abdominal pain, dyspepsia, myalgia, arthralgia, polyneuropathy</td>
<td></td>
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IV: intravenous; po: per oral
aminations should be performed. Although corticosteroids are believed as the first line of treatment, immunosuppressive treatments can be applied in resistant cases.

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**REFERENCES**