NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

CASE REPORT/OLGU SUNUMU

Arch Neuropsychiatry 2020;57:160–164
https://doi.org/10.5152/npa.2017.22732

Two New Cases and Literature Review of CLIPPERS Syndrome with Long-Term Follow-up

İki Yeni Olgu Sunumuyla Uzun Süre Takip Edilen CLIPPERS Sendromu

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ABSTRACT

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory disorder of the central nervous system. The pathophysiology of CLIPPERS is unknown. The disease has characteristic radiological lesions located in the pons, bulbus, and cerebellum. Here we report two new cases and review the literature on CLIPPERS syndrome. A 35-year-old woman presented with a 2-month history of progressive double vision, vertigo, gait ataxia, nausea, and vomiting. The second case was that of a 40-year-old Iraqi man who presented with a 3-month history of vertigo, headache, and gait ataxia. Diagnosis of CLIPPERS was established based on findings of punctate, nodular enhancing lesions in the pons and bulbus in the first case and in the cerebellum in the second. Our patients responded well to steroid therapy and remained relapse-free for 2 years. CLIPPERS is a rare autoimmune disorder with characteristic radiological findings. Long-term immunosuppressive therapy is necessary for treatment.

Keywords: CLIPPERS syndrome, brainstem, immunosuppressive therapy, corticosteroids

ÖZ

CLIPPERS sendromu merkezi sinir sisteminin inflamatuvar bir hastalığıdır. Patofizyolojisi bilinmemektedir. Hastalık pons, bulbus ve serebelluma lokalize karakteristik radyolojik lezyonlara sahiptir. İki yeni olguyla CLIPPERS sendromunu gözden geçirmeyi planladık. 35 yaşında kadın hasta 2 aydır devam eden ilerleyici çift görme, baş dönmesi, yürüyüş ataksisi, bulantı ve kusma şikayetleri ile geldi. İkinci vaka 3 aydır devam eden baş dönmesi, baş ağrısı ve yürüyüş ataksisi şikayetleri ile gelen 40 yaşında Iraklı erkek hastaydı. CLIPPERS tanısı ilk vakada pons ve bulbusta, ikinci vakada ise serebellumda punktat, nodüler kontrastlanan tipik lezyonlarla ve tanı kriterleri ile konuldu. Hastalarımız steroid tedavisine iyi yanıt verdiler ve 2 yıl boyunca nüks gözlenmedi. CLIPPERS sendromu karakteristik radyolojik bulguları olan nadir bir otoimmün hastalıktır. Uzun dönem immünsupresif tedavi gerekmektedir..

Anahtar Sözcükler: CLIPPERS sendromu, beyinsapı, immünsüpresif tedavi, kortikosteroidler

Cite this article as: Kamışlı Ö, Tecellioğlu M, Erbay MF, Kamışlı S, Özcan C. Two New Cases and Literature Review of CLIPPERS Syndrome with Long-Term Follow-up. Arch Neuropsychiatry 2020;57:160-164.

INTRODUCTION

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) was first described in 2010 by Pittock et al. (1). The pathogenesis of CLIPPERS is poorly understood. The initial symptoms are usually diplopia, ataxia, and facial paresthesia. Nystagmus, dysarthria, dysphagia, and other symptoms may occur (1,2). Magnetic resonance imaging (MRI) shows punctate, nodular gadolinium enhancement with a "pepper-like" appearance in the pons, midbrain, and cerebellum. Another important feature of CLIPPERS is the clinical and radiological response to glucocorticosteroids (GCS); withdrawal of GCS treatment may cause relapse (1,2,3). Other treatments include immunosuppressive agents (4). Differential diagnoses include cerebral lymphoma, neuro-Behçet's disease, pontine gliomas, intravascular lymphomatosis, neurosarcoidosis, and primary angiitis of the central nervous system (CNS). Comprehensive laboratory and radiological examinations are needed for diagnosis (1,2,3,4,5).

Here, we present two new cases in which clinical and radiological findings were consistent with those of CLIPPERS syndrome and their 2-years follow-up data.

CASE PRESENTATION

Case 1

A 35-year-old woman presented with a 2-month history of gradually progressive double vision, vertigo, gait ataxia, nausea, and vomiting. She had lost 10 kg during this period because of nausea and vomiting. The patient denied any past neurological symptoms, and there was no family history of neurological disorders. Her vital signs were within normal limits and a routine physical examination was unremarkable. The neurological examination showed bilateral sixth cranial nerve palsy and gait ataxia. Deep tendon reflexes were obviously increased. Babinski's sign was bilaterally positive.

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Received/Geliş Tarihi: 05.05.2017, **Accepted/Kabul Tarihi:** 06.07.2017, **Available Online Date/Çevrimiçi Yayın Tarihi:** 08.11.2017

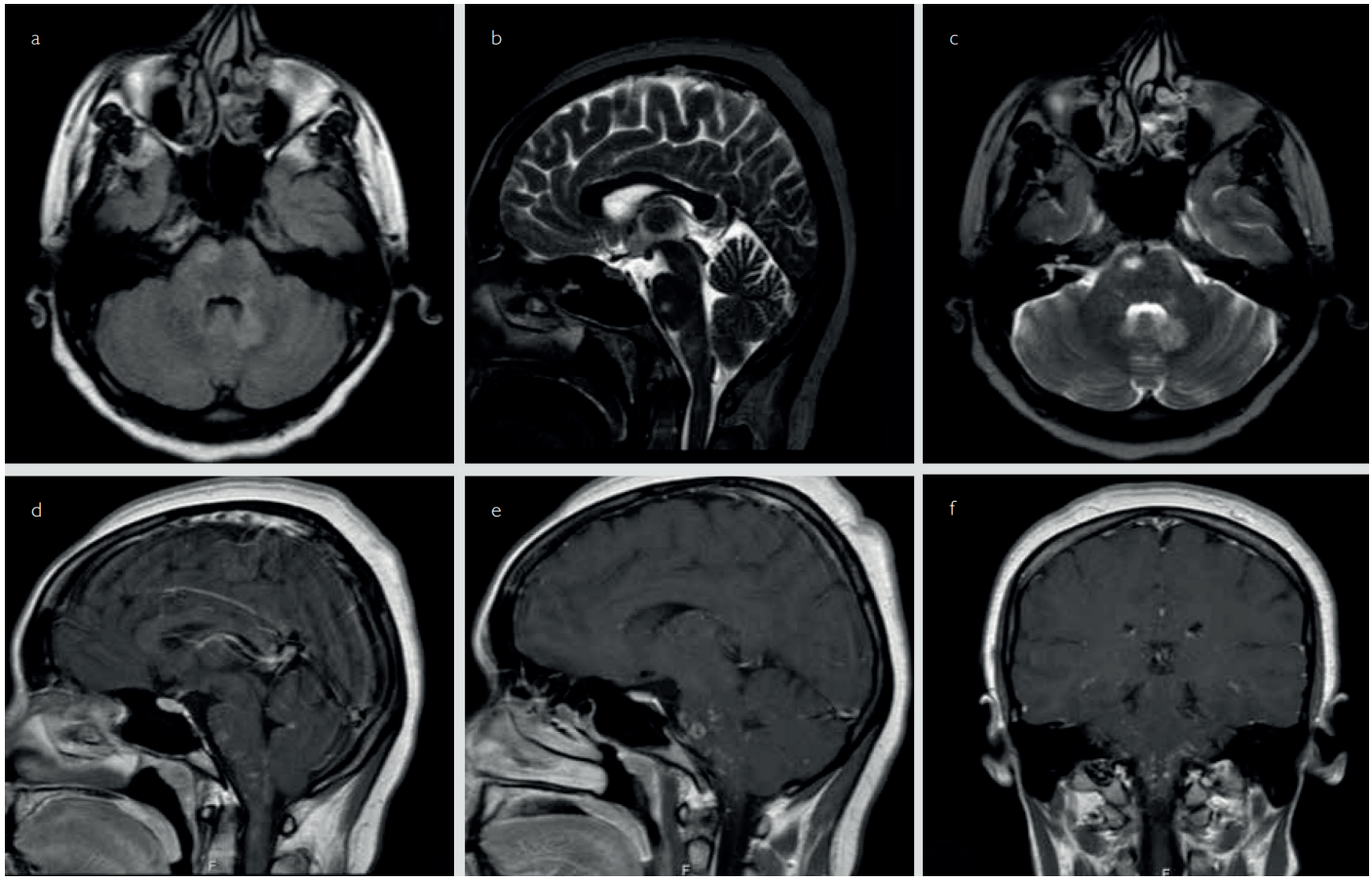

Figure 1. a-f. Brain MRI lesions of the first case. Axial FLAIR (a), Sagittal T2 (b), Axial T2 (c) weighted MR images show hyperintensities in the brainstem. Sagittal post contrast (d, e), Coronal T1 post contrast (f) weighted MR images show contrast enhancement pattern of first case

Cranial computed tomography (CT) was unremarkable, as was brain magnetic resonance (MR) angiography and MR venography. Brain MRI (Figure 1a-c) revealed ill-defined areas of T2- and fluid-attenuated inversion recovery (FLAIR) hyperintensities in the pons, bulbus, and left middle cerebellar peduncle. There was no mass effect or significant vasogenic edema. On postcontrast images, 1- to 3-mm punctate linear-nodular enhancement was seen within the T2 and FLAIR hyperintensities in the sagittal and coronal post-contrast images (Figure 1d-f). On MR spectroscopy (MRS), the N-acetyl aspartate/creatine (NAA/Cr) ratio decreased and Choline/Creatine (Cho/Cr) ratio slightly increased in the pons and bulbus, suggesting demyelination. Cervical MRI findings were normal.

Routine blood test results were within normal limits, including complete blood count, biochemistry parameters, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), thyroid function tests, and vitamin B12. Autoimmune screening was negative, including antinuclear antibodies ANA, Anti-neutrophil cytoplasmic antibody (ANCA), Romatoid Factor (RF), antiphospholipid antibodies, anti-Ro/SSA and La/SSB antibodies, and anti-neuronal antibodies (anti-Hu, anti-Yo, anti-Ri, and anti-NMDA antibodies). Cerebrospinal fluid (CSF) analysis demonstrated elevated protein level (53.1 mg/dL, normal range: 15-45 mg/dL) and elevated cell count (leukocyte: 50 cells/mm3; lymphocyte: 100%). Glucose and chloride levels were normal. Cytology test with flow cytometry was negative for malignant and lymphoma cells. CSF cultures for tuberculosis and fungi were negative, and polymerase chain reaction (PCR) for viruses (including herpes simplex virus types 1 and 2, enterovirus, herpes zoster virus, cytomegalovirus, and Epstein-Barr virus, Brucella, parvovirus B19) were negative. The patient tested negative for aquaporin 4 antibody. There were no oligoclonal bands in the CSF. Syphilis, human immunodeficiency virus (HIV), and Brucella tests were also negative. There were no clinical signs of neuro-Behçet's disease, and the pathergy test was negative. Tumor markers were negative. Serum calcium and Angiotensin Converting Enzyme (ACE) levels were normal. CT findings of the thorax and abdomen were normal; it did not show any lymphadenopathy or other abnormalities suggestive of lymphoma, primary neoplasm, or systemic sarcoidosis.

With characteristic imaging findings and typical clinical presentation (ataxia and diplopia), CLIPPERS syndrome seemed to be the most likely diagnosis. The patient was administered intravenous methylprednisolone (1 g/day) for 10 days and was then switched to oral methylprednisolone (64 mg/day); oral methylprednisolone dose was gradually tapered to 24 mg/day and was continued at this dosage for 6 months. Azathioprine (100 mg/day) was administered as a corticosteroid-sparing agent in the third month of the treatment. Then, the oral steroid was tapered and discontinued. Symptoms completely resolved after the steroid treatment. MRI showed resolution of the gadolinium-enhancing lesions after 3 months of immunosuppressive therapy. Repeat MRI (Figure 2a-c) and MRS showed complete resolution of the gadolinium-enhancing lesions and recovery of NAA/Cr ratio in the pons and bulbus. The patient was still administered azathioprine (100 mg/day). She has remained stable without symptoms. No relapses have been observed in the 24 months after her treatment.

Case 2

A 40-year-old Iraqi man presented with a 3-month history of vertigo, headache, and gait ataxia. He had no past neurological symptoms, and

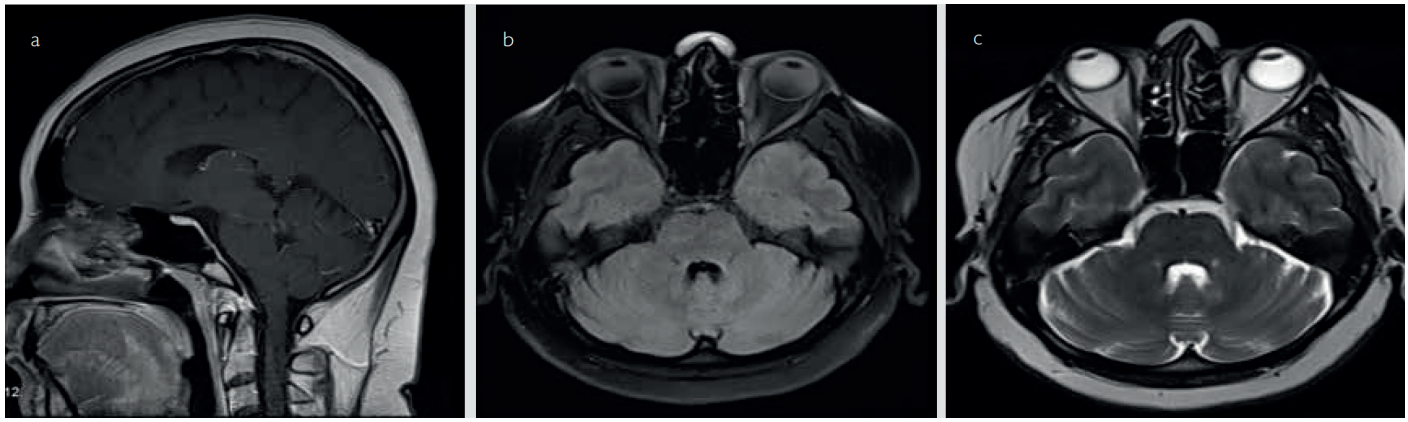

Figure 2. a-c. MRI of the first case at 3 months after corticosteroid therapy showing dramatic reduction in the extent of gadolinium-enhanced lesions. Sagittal FLAIR (a), Axial FLAIR (b), Axial T2 (c) weighted MR images

there was no family history of neurological disorders. His vital signs were within normal limits, and a routine physical examination was normal. The neurological examination showed only mild gait ataxia.

Cranial CT, brain digital subtraction angiography, and MR venography findings were normal. Brain MRI (Figure 3a-c) showed T2 and FLAIR hyperintensities in both cerebellar hemispheres. On postcontrast images, 1- to 3-mm punctate linear-nodular enhancement was observed within the areas of T2 and FLAIR hyperintensities in brain MRIs (Figure 3d-f). MRS showed decreased NAA/Cr ratio and a slightly increased Cho/Cr ratio in the pons and bulbus, suggesting demyelination.

Routine blood test results were normal, including complete blood count, biochemical parameters, CRP, ESR, thyroid function tests, and vitamin B12. Autoimmune markers were negative.

Cerebrospinal fluid analysis showed lymphocytic pleocytosis (leukocyte: 20 cells/mm3; lymphocyte: 100%) and an elevated protein level (60 mg/dL, normal range: 15-45 mg/dL). Glucose and chloride levels were normal. Cytology test was negative for malignant and lymphoma cells. CSF cultures for tuberculosis and fungi were negative and PCR results for viruses were negative. Syphilis, HIV, and Brucella tests were also negative. There were no clinical signs of neuro-Behçet's disease and the pathergy

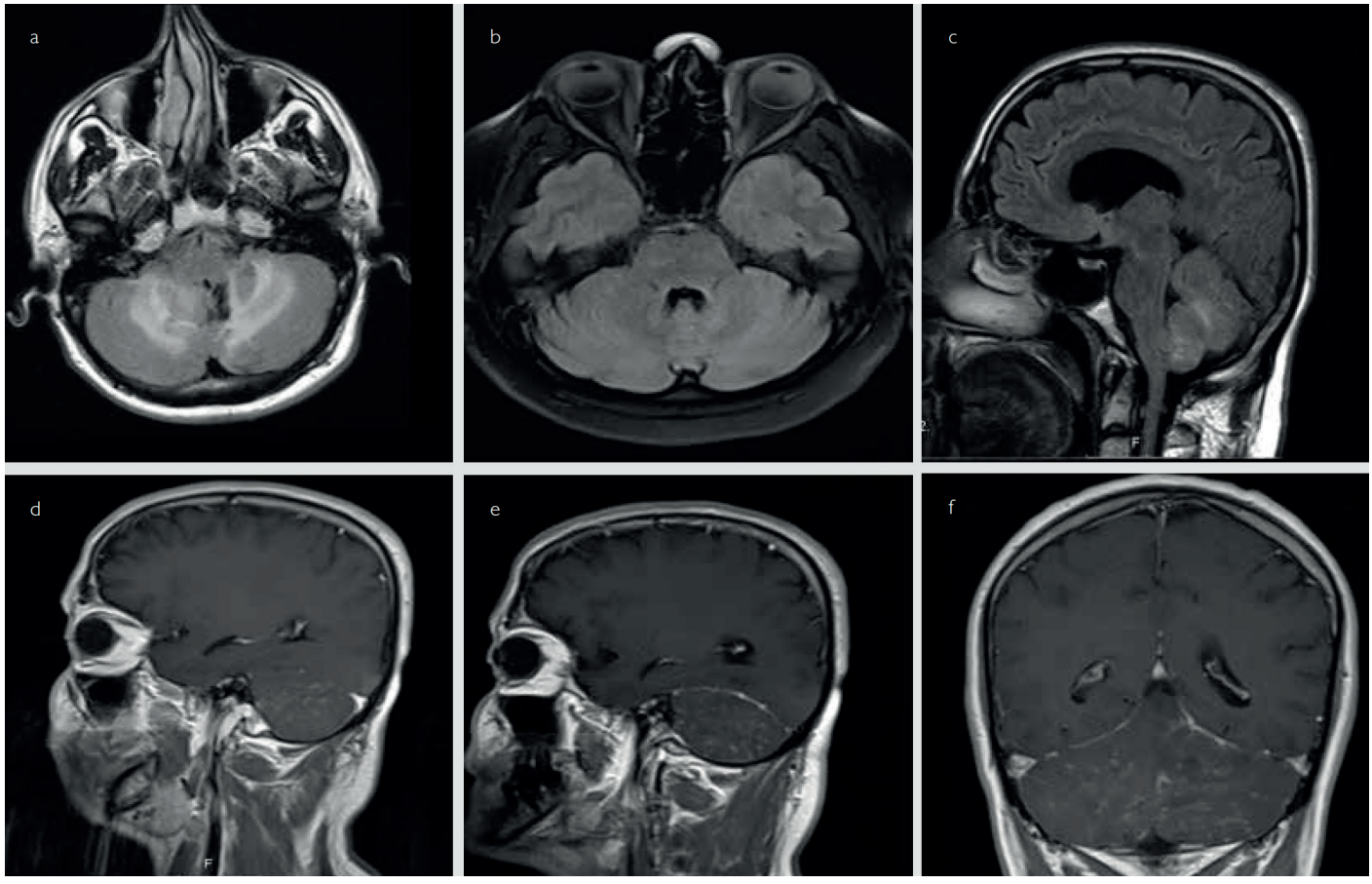

Figure 3. a-f. Brain MRI lesions of the second case. Axial FLAIR (a,b), Sagittal flair (c), Sagittal post contrast(d) and Coronal T1 post contrast(f) weighted MR images show the lesions of second case

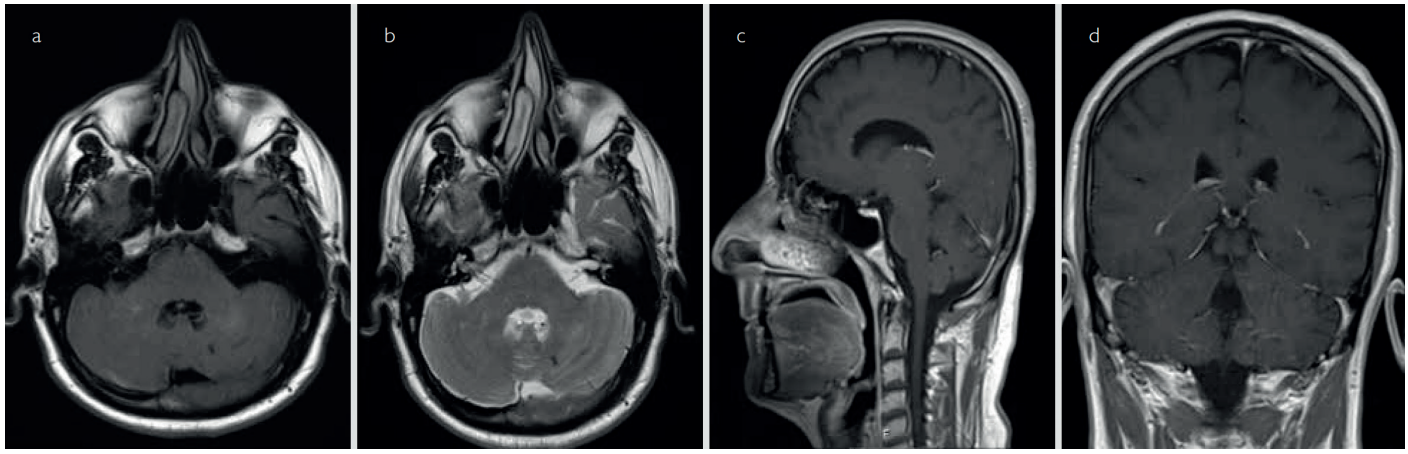

Figure 4. a-d. Brain MRI at 4 months after restarting corticosteroids showing dramatic reduction in the extent of gadolinium-enhanced lesions in second case. Axial FLAIR (a), Axial T2 (b), Sagittal postcontrast (c) and Coronal T1 post contrast (d) weighted MR images show the resolution of lesions

test was negative. Tumor markers were negative. CT findings of the thorax and abdomen were normal. Positron Emission Tomography (PET) CT findings were also normal.

After excluding other diagnoses, CLIPPERS syndrome was the most likely diagnosis. The patient was treated with intravenous methylprednisolone (1 g/day) for 7 days and was then switched to oral methylprednisolone (80 mg/day); the dose was gradually tapered until he remained on 20 mg/day for 6 months. Azathioprine (100 mg/day) was also administered. Symptoms resolved after steroid use. MRI showed marked resolution of the gadolinium-enhancing lesions after 4 months of immunosuppressive therapy (Figure 4a-d). He remained stable for 2 years, until he moved to another country and was lost to follow-up.

Both patients gave informed written consent for the publication of this report.

DISCUSSION

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids syndrome is a pontine-centered inflammatory disorder with an uncertain etiology. The clinical diagnosis of CLIPPERS is usually based on clinical, radiological, and pathological findings and the response to GCS (1,2,3,4,5,6). A clinical diagnosis based on the appearance of a characteristic image is important, but clinicians should still consider differential diagnoses and exclude similar CNS inflammatory disorders (1,7).

Various autoimmune diseases have similar neurological symptoms. Serological markers and radiological features can help in diagnosing disease. The differential diagnoses of CLIPPERS include neurosarcoidosis, CNS lymphoma, lymphomatoid granulomatosis, CNS vasculitis, Sjogren's syndrome, systemic lupus erythematosus (SLE), Bickerstaff brainstem encephalitis, paraneoplastic disease, chronic perivascular infectious processes (tuberculosis, neurosyphilis, Whipple's disease, and parasitic infection), gliomas, CNS demyelinating disease, multiple sclerosis (MS), Neuro-Behçet's disease, and histiocytosis, including Langerhans cell histiocytosis (2,3,4,5,6,7,8,9).

Cerebrospinal fluid analysis plays a key role in diagnosing CNS inflammatory diseases. In SLE, the patients' serology is usually positive (9). Our patient's serology was negative. Neuro-Behçet's disease was also excluded. The patients denied having any genital or oral ulceration. There were no signs of Behçet's disease, and both patients had negative pathergy tests. Microbiology test results revealed no infections. Both our patients had negative CSF cytology and negative PCR parameters. It is important to make differential diagnosis with syphilis, HIV, and brucellaosis. The results of the test of syphilis, HIV, and brucella were also negative. There were no clinical signs or systemic features such as meningism and fever that suggested an infection. The serum calcium and ACE levels were normal, and chest tomography was also normal. Based on these results, neurosarcoidosis was also excluded. The diagnosis of MS was also less likely given the lack of typical attacks and MRI lesions. Tumor markers were negative, and no tumors were found in detailed investigations.

Central nervous system lymphoma is an another differential diagnosis for CLIPPERS and may also have a similar pattern. However, CSF cytology using flow cytometry was negative in CLIPPERS. MRS may also help in making a differential diagnosis. In CNS lymphoma, MRS has a high Cho/NAA ratio. On MRS, the NAA/Cr ratio decreased and the Cho/Cr ratio slightly increased in the pons and bulbus, suggesting demyelination in our patients. CNS lymphoma patients have atypical radiologic presentations and can also respond well to steroids (2). The difference between CNS lymphoma and CLIPPERS is difficult. Taieb et al. (10) reported a case of CNS B-cell lymphoma 2 years after the first diagnosis of CLIPPERS. They had a biopsy before CLIPPERS was diagnosed. However, the patient was eventually diagnosed with CNS lymphoma. In our cases, we did not perform biopsy because it is an invasive procedure and the patient had responded well to steroids. Brain biopsy is necessary if alternative etiologies cannot be ruled out with detailed investigations, if atypical clinical or neuroimaging findings are present, or if the patients are medically resistant to steroids (10,11).

The pathogenesis of CLIPPERS is unknown. Researchers have suggested that CLIPPERS is an autoimmune disorder caused by inflammatory infiltration in the perivascular regions where possible targeted autoantigens are present. However, this hypothesis is incomplete because the specific mechanism remains unclear (1,2,8,9,10,12,13). According to cases that have been reported, the onset age of CLIPPERS syndrome ranges from 13 to 86 years. The mean age is 50.2 years. Both genders can be affected (2).

There are no serum biomarkers to confirm the diagnosis of CLIPPERS; the diagnosis is often based on imaging findings. The main features of the disease are episodic symptoms associated with the brainstem that dramatically respond to steroids (8,11,14). The radiological findings in both our patients were consistent with CLIPPERS.

Pulse steroid therapy should be initiated as soon as possible to reduce clinical deterioration with relapse (1,15). Taieb et al. (16) reported no

recurrence in seven patients with a mean follow-up of 5 years and daily prednisolone dose of ≥20 mg. In the long term, steroid-sparing agents may be a better option (4,14). Maintenance treatment is important to prevent further relapses. We administered 1 g daily for 7-10 days and then switched to oral methylprednisolone at 1 mg/kg daily. In our cases, azathioprine (100 mg/day) was administered as a corticosteroid-sparing agent when methylprednisolone was tapered to 20 mg/day and the patients' conditions were stable. We then used azathioprine as a monotherapy after oral methylprednisolone was discontinued. Azathioprine without GCS may be effective for maintaining remission (12). Although corticosteroid-sparing agents are aimed to reduce the dose of corticosteroids in view of their multiple side effects, a majority of patients use oral corticosteroids alone to maintain remission (2). Suer et al. (12) reported a case who was receiving azathioprine as the main treatment without GCS; follow-up clinical and radiological investigation results in the 3rd, 6th, and 12th months were normal. Gabilondo et al. (15) attempted to taper GCS to 5 mg/ day and to use intravenous immunoglobulins (0.4 g/kg/day for 5 days) for a patient, but the patient's symptoms reappeared in 2 days after administering the last dose of intravenous immunoglobulins. Taieb et al. (17) observed 42 relapses among 12 patients in a mean follow-up period of 5.5 years. Relapses are provoked by withdrawing or tapering GCS below a lower dose limit. The duration of treatment is unclear. We continued to follow-up our cases for 2 years, with the first case still being followed up. Long-term GCS treatment seems necessary for most patients with CLIPPERS. Further studies should help determine the duration of this immunosuppressive treatment.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.K., M.F.E., C.O.; Design - O.K., S.K., M.T.; Supervision - C.O.; Resource - O.K., M.T., M.F.E.; Materials - O.K., M.T.; Data Collection and/or Processing - O.K., S.K., M.F.E.; Analysis and/or Interpretation - C.O.; Literature Search - M.T., S.K., O.K.; Writing - O.K., M.T.; Critical Reviews - C.O., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - O.K., M.F.E., C.O.; Tasarım - O.K., S.K., M.T.; Denetleme - C.O.; Kaynaklar - O.K., M.T., M.F.E.; Malzemeler - O.K., M.T.; Veri Toplanması ve/veya İşlemesi - O.K., S.K., M.F.E.; Analiz ve/veya Yorum - C.O.; Literatür Taraması - M.T., S.K., O.K.; Yazıyı Yazan - O.K., M.T.; Eleştirel İnceleme - C.O., S.K

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir

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