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CORRESPONDENCE

A Case Report of CLIPPERS (Chronic Lymphocytic Inflammation with Pontocerebellar Perivascular Enhancement Responsive to Steroids) Syndrome

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Introduction

Chronic lymphocytic inflammation with pontocerebellar perivascular enhancement responsive to steroids (CLIPPERS) syndrome is a recently described central nervous system (CNS) disorder characterized by distinctive radiological and clinical features [1]. It is a pontine-centric disorder [1] with typical imaging features consisting of symmetric curvilinear gadolinium enhancement peppering the pons, cerebellum, and adjacent structures [1–3]. Almost all patients with CLIPPERS syndrome have clinical symptoms related to the involvement of brainstem and cerebellum [1–3]. Subacute gait ataxia, diplopia, and cerebellar dysarthria are the cardinal clinical features in the majority of cases with CLIPPERS [1–3]. Immunopathological studies of patients with CLIPPERS syndrome have shown a characteristic, but nonspecific, severe perivascular T-cell-predominant infiltrate, without apparent pathological findings of other known infectious, inflammatory, or demyelinating diseases [1, 2]. There is an ongoing discussion whether CLIPPERS is a syndrome or an entity, because no specific biomarker for CLIPPERS has been identified yet, and a body of increasing evidence show that this disorder overlaps with other syndromes [4, 5]. Although the exact pathophysiological mechanism of this syndrome has not been fully elucidated, neuropathological findings and the clinical response to immunosuppressant agents, especially steroids, suggest an autoimmune or other inflammation mediated pathogenesis [1]. Herein, we present a new case with the clinical and radiological findings consistent with CLIPPERS syndrome.

Case Report

A previously healthy 51-year-old man presented with severe and progressive limb and extremity ataxia, diplopia, and left-sided weakness. His initial complaints started 3 months prior to admission. Neurological examination revealed ataxic dysarthria, horizontal and vertical nystagmus with severe gait and extremity ataxia, horizontal gaze palsy, and left-sided paresis (Medical Research Council strength score grade 4). Cranial magnetic resonance imaging (MRI) showed multiple punctate hyperintensities in T2-weighted images, with curvilinear contrast enhancement on T1-weighted images within the pons, midbrain, and cerebellum (Fig. 1a, b). MRI scans of the spinal cord showed involvement of the upper cervical region (Fig. 1c). Differential diagnosis included CNS vasculitis, CNS lymphoma, CNS infections, demyelinating diseases, paraneoplastic syndromes, sarcoidosis, tuberculosis, and CLIPPERS syndrome. There were no clinical findings suggestive of vasculitis. Cranial and cervical magnetic resonance angiographies were normal. Complete blood count, erythrocyte sedimentation rate (ESR), chest X-ray, and serum biochemistry revealed no abnormalities. In his cerebrospinal fluid (CSF) examination, the opening pressure, protein and glucose lev-

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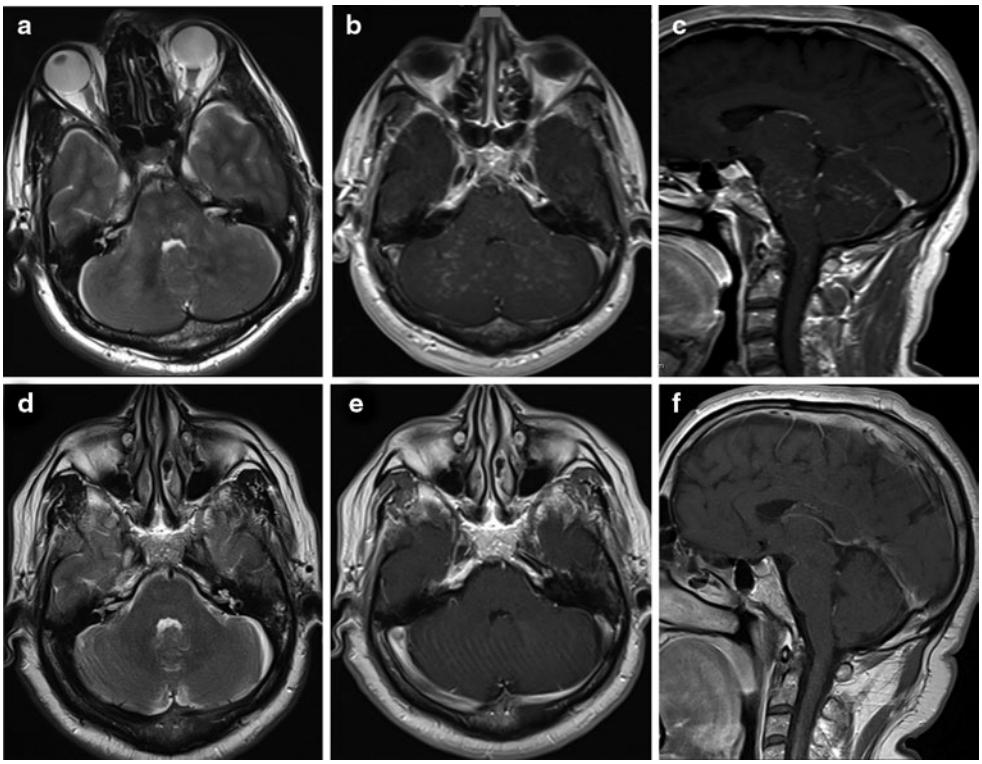

Fig. 1 Magnetic resonance imaging of brain and cervical spinal cord before (**a**–**c**) and after (**d**–**f**) corticosteroid treatment. Characteristic punctate hyperintense lesions in the pons and cerebellum (**a**, axial T2-weighted images) with curvilinear gadolinium enhancement in T1 weighted images (**b**). Similar contrast enhancement is shown in cervical spinal cord (**c**). All of these findings resolve after corticosteroid treatment (**d**–**f**)

els were found to be within normal limits (150 mm H_2O, 39 mg dl^{-1} and 65 mg dl^{-1}, respectively). While microscopic examination of CSF revealed 2 leukocytes/mm^3 (upper limit of normal is 5 leukocytes/mm^3), CSF cytology revealed no malignant cells. Immunoglobulin G (IgG) index was normal (0.04) and three IgG oligoclonal bands were detected by isoelectric focusing. The serum and/or CSF was negative for any infectious disorder including HIV, EBV, CMV, HSV, VZV, VDRL, rubella, toxoplasmosis, syphilis, and Lyme serology. Cultures of blood, urine, and CSF were all negative. Immunological study, which consisted of antinuclear antibodies (ANA), antiextractable nuclear antigen (ENA), anti-double stranded DNA antibodies (Anti-ds DNA), antineutrophil cytoplasmic antibody, and serum angiotensin converting enzyme (ACE) were all negative. Onconeural antibodies (i.e., Anti-Hu, Anti-Yo, Anti-Ma, Anti-Amphiphysin) were not detected and there was no elevation in tumor marker levels. Scrotal ultrasonography (USG) and thoracoabdominal computerized tomography (CT) revealed no abnormalities. The patient was treated with high-dose intravenous methylprednisolone (1 g/day, for 5 days) followed by oral prednisolon therapy at an initial dose of 60 mg (1 mg/kg). The corticosteroid therapy resulted in marked neurological improvement within 7 days and the patient's clinical findings returned to normal limits within 1 month. MRI of the brain and spinal cord in the following month showed dramatic improvement in radiological findings (Fig. 1d–1f). Oral corticosteroid treatment was tapered 8 weeks after initiation and discontinued after 6 months, while azathioprine therapy (2 mg/kg/day) was started as a corticosteroid sparing agent on the 2nd month of the treatment scheme. Follow-up clinical and radiological investigations at the 3rd, 6th and 12th months were normal and the patient is still on azathioprine treatment (1 mg/kg/day) on the 12th month of his initial symptoms.

Discussion

Subacute and progressive cerebellar and brainstem symptoms with characteristic MRI features showing punctate enhancement peppering the pons with similar lesions in the medulla, midbrain, and cerebellum are the hallmarks of CLIPPERS syndrome [1–7]. Spinal cord involvement has been reported in several cases [1–3]. Both clinical and radiological findings show dramatic response to steroid therapy [1–3, 6, 7]. Our patient showed similar features of this syndrome.

CLIPPERS syndrome was first described in eight patients in 2010 by Pittock et al. [1]. Besides unique clinical and radiological features, the authors also reported the neuropathological abnormalities in these patients. Half of the patients had brain biopsies and each case showed similar findings of marked lymphocytic infiltrate in the white matter with perivascular predominance, but also a more diffuse parenchymal inflammatory infiltrate. Neither of these patients had myelin abnormality, nor characteristic findings of lymphoma, vasculitis, sarcoidosis, lymphomatoid gran-

ulamatosis, or infectious processes [1]. Since then, similar pathological findings have been reported in several studies [1–3]. Thus, brain biopsy is recommended only in patients who are unresponsive to steroid therapy or in patients when alternative diagnoses remains likely [1]. We did not perform a biopsy in our patient because the patient had very similar findings to patients described in the literature. In addition, we excluded all the possible inflammatory, neoplastic, paraneoplastic, vasculitic, demyelinating, and infectious disorders by detailed clinical, radiological, and serological investigations.

In each patient with suspected CLIPPERS syndrome, neurosarcoidosis, CNS lymphoma, multiple sclerosis, infectious diseases, and CNS vasculitis should be ruled out with diagnostic tests including ACE, ESR, ANA, Anti-ds DNA, ENA profile, bacterial, viral, fungal serologies, CT of chest and abdomen, PET scan, testicular USG, mammography, and CSF evaluation [1–3]. If brain biopsy is performed, lymphocytic infiltration predominantly composed of CD3 reactive T lymphocytes and some CD 20 positive B lymphocytes is detected [1]. Patients are treated with steroids initially and maintained with other immunosuppressive agents to sustain clinical improvement [1–3]. Our case fulfilled criteria of CLIPPERS syndrome with clinical, radiological, and treatment entities, so brain biopsy was not performed.

The natural history of CLIPPERS syndrome is not clear, but a very high risk of relapse during the reduction or cessation of corticosteroids has been reported [1–3]. Atrophy in the brainstem, cerebellum, or spinal cord has been shown in some patients with CLIPPERS syndrome and long-term disability correlates with the severity of previous relapses [3]. Therefore, aggressive early treatment with high doses of corticosteroids and maintenance therapy with immunosuppressive agents seems to be logical [1–4].

In summary, as a recently defined syndrome, any reported case is implemental in increasing the awareness of this disorder. Any new data would alleviate our understanding of the natural course and treatment of the disease.

Conflict of Interest None of the authors have any direct or indirect conflicts of interest, financial or otherwise, related to the subject matter contained in this report.

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