CLIPPERS: Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids

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ABSTRACT

A novel type of brainstem-predominant encephalomyelitis was first described as chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) in 2010 by Pittocket al and then few additional patients were reported. Here we report a 50-year-old Iranian male who presented with a number of clinical features described as typical for CLIPPERS. The association of typical clinical presentation and typical MR imaging could be sufficient for a reliable diagnosis of CLIPPERS.

Keywords: Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive To Steroids; CLIPPERS; Brainstem; Corticosteroid; Perivascular Infiltration

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INTRODUCTION

CLIPPERS syndrome (Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids) is a recently described CNS inflammatory disorder [1]. Since 2010, several new possible cases have been published [2-18]. CLIPPERS was considered as a distinct disease of unknown aetiology by its original describers. Its key features are: 1) episodic, subacutely progressive cerebellar ataxia as a cardinal symptom as well as diplopia and dysarthria in the majority of cases [1–3], 2) characteristic bilateral, multifocal punctate or curvilinear gadolinium enhancing MRI lesions, predominantly affecting the pons and extending into adjacent brain regions, 3) white matter perivascular lymphohistiocytic infiltration, dominantly by CD4+ T cells and macrophages, with a variable extent of parenchymal inflammation, 4) steroid responsiveness of the symptoms, and 5) the absence of evidence for alternative diagnoses. We report a new patient with features consistent with this syndrome.

CASE PRESENTATION

In November 2012, a 50-year-old Iranian man was admitted with a two months history of progressive disequilibrium, tinnitus and hyperacusis. Binocular horizontal diplopia, right side facial numbness and change in taste sensory was added to his symptoms from 2 weeks prior to admission. On initial neurological examination, he showed bilateral six nerve palsy, right peripheral facial palsy and decrease in light touch and pin prick sensation in the right side of his face (in V3 territory). In cerebellar examination he had bilateral limb and gait ataxia specially in right limbs. Other sensory and motor examinations had no significant finding.

Cerebrospinal fluid (CSF) examination demonstrated a raised protein level (64 mg/dl, normal <40 mg/dl) with normal glucose and cell count. The following CSF investigations were normal or negative: culture, oligoclonal band antibody, ACE level, cytology, Indian ink. Serum anti-EBV-VCA- Ig G, anti-CMV Ig G, anti-HIV antibody (1 & 2), HBs Ag, anti-HCV antibody, VDRL and anti-Brucella Ig M and Ig G were negative and CBC, serum electrolyte, liver function test, BUN, creatinine, C3, C4, CH50, NA, Anti-*dsDNA antibodies*, lupus anticoagulant, *anticardiolipin* antibody, ANCA (C & P), Antiglyadin antibody, B12 level were in normal

range. Digital subtraction angiography was normal too.

A cranial MRI showed bilateral T2-hyperintense and contrast-enhancing lesions scattered throughout the pons, cerebellar peduncle and cerebellum. The most affected area was the cerebellar white matter, while the pons showed only minor involvement as reported by Buttmann et al (Figure 1).

Based on the assumption of an immune-mediated subacute encephalomyelitis, methylprednisolone intravenously was administered 1gr/day over 5 days, followed by oral steroid administration (prednisolone, 60 mg/day) and azathioprine 50 mg/day. A rapid complete clinical and partially imaging improvement obtained (Figure 2). After 2 years, oral prednisolone and azathioprine were slowly tapered off.

DISCUSSION

CLIPPERS manifests characteristically in a subacute manner and presents usually with a varying symptomatology related to brainstem, cranial nerve

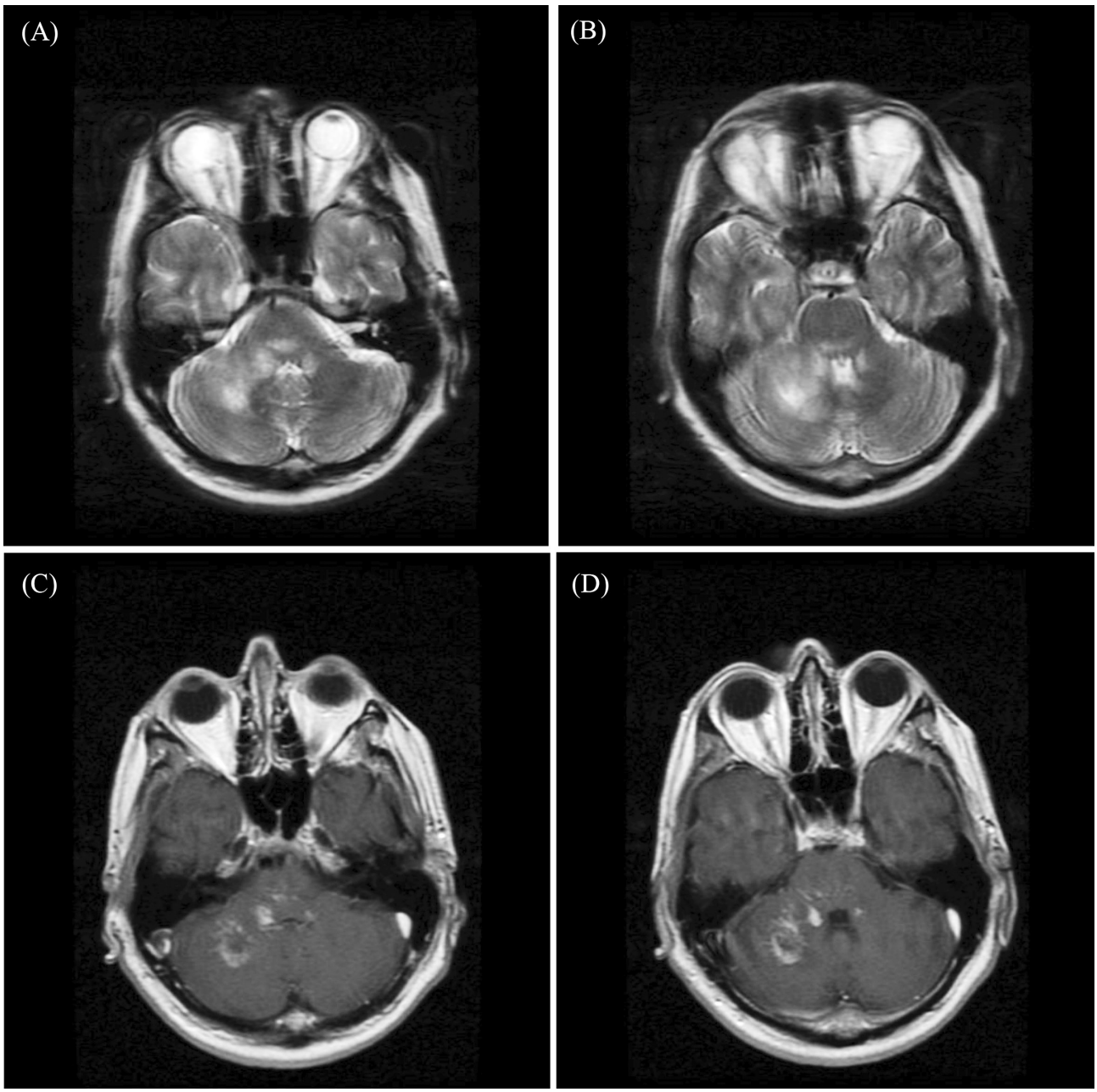

Figure 1. Conventional brain MRI shows pontine and cerebellar patchy T2-hyperintense (A & B) areas associated with punctuate and curvilinear contrast-enhancement in T1-weighted images (C & D).

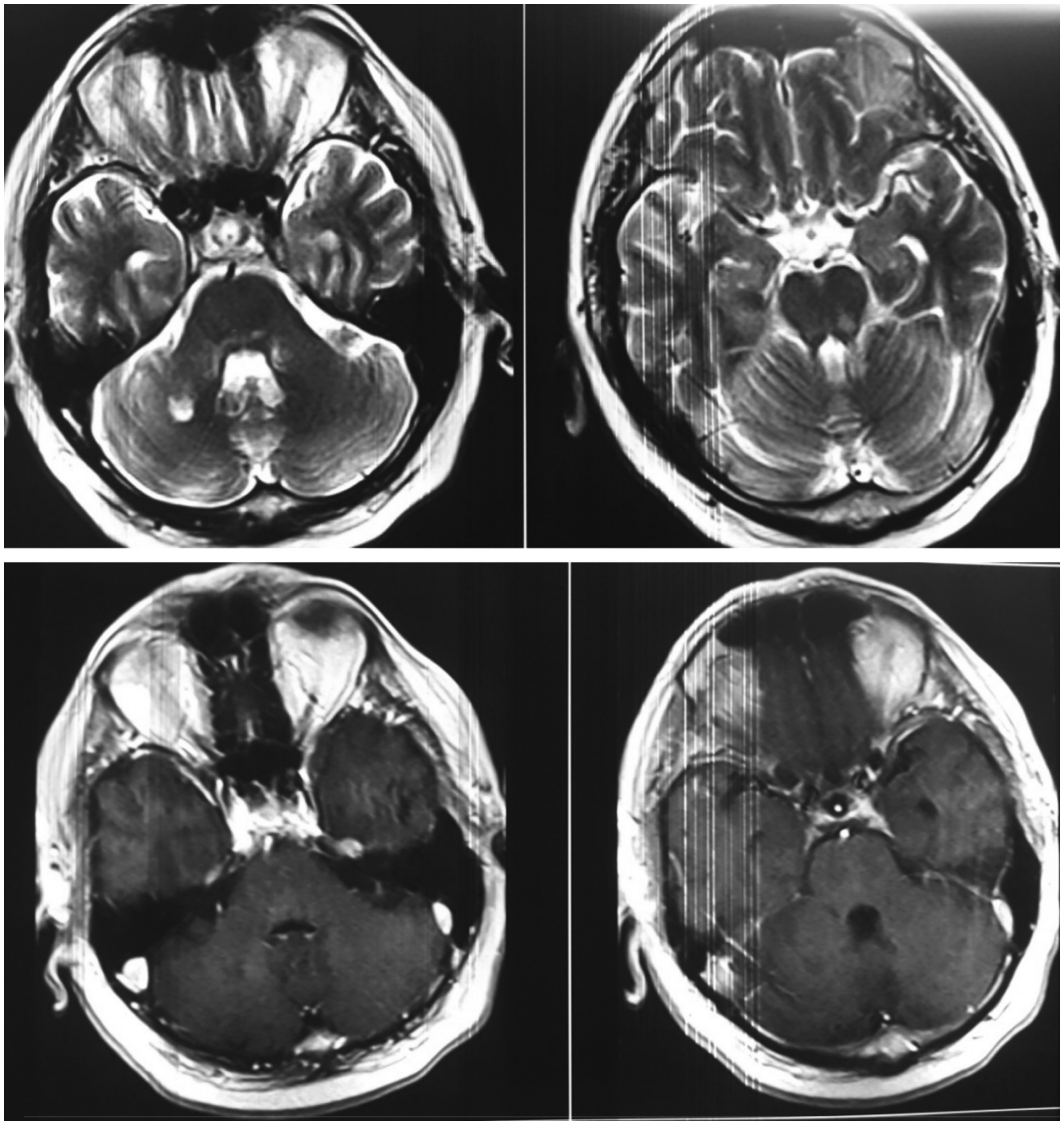

Figure 2. Imaging improvement after steroid therapy (about 11 month after first MRI).

and/or cerebellar involvement, frequently including gait ataxia, dysarthria, diplopia and/or altered facial sensation. An overview on clinical characteristics described in CLIPPERS patients is shown in Table 1. Clinical manifestations may be heterogeneous, multi-faceted and variable in individual cases, but comprise essentially the following [10]. Commonly prominent symptoms related to multilocular brainstem including cranial nerve and cerebellar involvement, which may present in various combinations or rarely in isolation (e.g. ataxia, dysarthria, oculomotor abnormalities, tingling of the face, vertigo) [1,2,5,6,9,10,13,15].

Our intensively characterized patient showed a number of features described as typical for CLIPPERS: 1) a steroid-responsive episodic course of gait ataxia and/or double vision, 2) MRI findings with small contrast-enhancing lesions "peppering" infratentorial and less also supratentorial brain regions compatible with CLIPPERS [4].

An MRI of brain showed multiple punctate hyperintensities in T2 weighted images, confined to the pons and cerebellum, with curvilinear gadolinium enhancement in T1 weighted images. The clinical and radiological features suggested the CLIPPERS syndrome.

The symptoms and MRI findings improved dramatically with high dose parenteral corticosteroids [14].

MRI findings in CLIPPERS show a very striking and characteristic lesion pattern and a high degree of similarity among affected individuals. Because the typical radiological picture is readily identifiable and represents a core criterion of CLIPPERS, brain and spinal cord

Table 1. Clinical features of CLIPPERS [10].

Symptoms/signs referable to brainstem, cranial nerve and/or cerebellar dysfunctions
• Ataxia (gait ataxia, stance ataxia, truncal ataxia, limb ataxia)
• Dysarthria
• Dysphagia
• Dysgeusia
• Diplopia/oculomotor abnormalities (oculomotor palsies, gaze palsy, internuclear ophthalmoplegia, one-and-a-half syndrome, disturbances of saccadic eye and slow eye pursuit)
• Nystagmus (spontaneous, gaze evoked, upbeat, downbeat, rotational nystagmus)
• Altered sensation or tingling of the face (facial tingling, par-/dysaesthesias, hypaesthesia), altered sensation of the scalp, palate or tongue
• Facial nerve palsy
• Vertigo, hyperacusis, hearing impairment, tinnitus
• Hoarse voice
• Tongue weakness
• Hiccup
• Nausea

MRI examinations play a crucial role in the diagnostic process [10].

Diagnosis of CLIPPERS is based on clinical, radiological, laboratory and CSF investigations and, if necessary, brain biopsy. Extensive investigations are mandatory to exclude alternative conditions that may mimic CLIPPERS syndrome. To date, validated diagnostic criteria for CLIPPERS are not available. Due to the varied clinical presentation and the potential for diagnostic confusion [2,10].

CONCLUSION

The diagnosis of the disease was formulated on the basis of typical MRI findings and its responsiveness to steroids in a 50-year-old Iranian man with subacute onset of ataxia and diplopia. According to previous publications the association of typical clinical presentation and typical MRI with exclusion of other diagnosis could be sufficient for a reliable diagnosis of CLIPPERS, even in the absence of brain biopsy [1,3].

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