Acute Lacunar Infarcts in CLIPPERS: Is the Chronic Infiltrative Lymphocytic Perivascular Disease Process to Blame?

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SUMMARY – *CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) is a recently described chronic inflammatory disorder involving the brainstem with characteristic imaging findings. Since it was originally described in 2002, only a handful of cases have been reported in the literature. We describe two additional cases of CLIPPERS with characteristic clinical and radiological findings. Besides the previously described MR findings, one of the cases also demonstrated multiple basal ganglia lacunar infarcts, a finding which has not been previously reported. We hypothesize that the lacunar infarcts are caused by this chronic infiltrative perivascular disease process.*

Introduction

CLIPPERS was originally described in 2002 as a disorder predominantly involving the pons and its surrounding structures⁶. The pattern of enhancement is unique and consists of a characteristic punctate and curvilinear enhancement throughout the pons and extending variably into the brachium pontis, midbrain and medulla. The clinical findings and pattern of enhancement of this disease in the brainstem are so striking that some authors have suggested that a pathologic diagnosis may not be needed and treatment with steroids can be instituted without the need for a brainstem biopsy⁶.

The two cases described in this case report had the characteristic imaging findings and clinical features of CLIPPERS. In addition, one of the cases also demonstrated multiple lacunar infarcts in the basal ganglia, which we hypothesize are caused by a concomitant primary perivascular disease process in the brainstem.

Case Reports

Case 1: A 53-year-old Caucasian man with history of seizure disorder, hypertension and substance abuse including cocaine, presented

to the emergency room with acute onset of dysarthria. On examination, the patient was also found to have truncal ataxia on standing, a wide-based gait, and decreased bilateral patellar and ankle reflexes. His medical history was significant for prior admissions secondary to substance abuse and hypertensive crises, likely due to drug abuse, controlled on medication. MRI of the brain performed on admission revealed diffuse brainstem T2/Flair signal hyperintensities with extension into the middle cerebellar peduncles (Figure 1). Underlying multiple foci of punctate and linear enhancement were noted in the brainstem, predominantly in the pons. No restricted diffusion was noted in the brainstem. Other relevant findings included multiple areas of restricted diffusion in the basal ganglia bilaterally and underlying punctate and linear foci of enhancement, patterns similar to that seen in the brainstem. An MRI performed on a prior admission five months previously had shown similar brainstem involvement but the degree of T2/Flair hyperintensity and the foci of nodular enhancement were less than on the current study, suggesting an interval increase in the disease process involving the brainstem.

Various differentials for the brainstem findings were considered including lymphoma, HIV, neurosyphilis, vasculitis and neuro-Behçet's

disease. Lumbar puncture was negative except for an increased CSF total protein of 62 mg/ ml. CSF flow cytometry was negative and no monoclonal B or T cell population was noted. No oli-

goclonal bands were noted in the CSF. Rapid plasma regain test for syphilis was negative. HIV testing was also negative. CD4 and CD8 counts were within normal limits. Vitamin B12

Figure 1 MRI of the brain: Axial FLAIR images at the level of the mid brain (A), pons (B), coronal post contrast T1-weighted (C,D) and sagittal post contrast T1-weighted (E,F) images and axial diffusion image (G) at the level of the basal ganglia. There is enlargement of the pons and the midbrain with underlying diffuse ill-defined FLAIR signal hyperintensity extending into the middle cerebellar peduncles (small black arrows). Post contrast images demonstrated multiple small areas of nodular and linear enhancement (small white arrows). No restricted diffusion was noted in the brainstem (not shown). Small areas of restricted diffusion consistent with acute lacunar infarcts were noted in the basal ganglia bilaterally (long white arrows). Corresponding subtle linear/nodular enhancement were also noted in the lenticulostriate regions bilaterally in a perivascular distribution (long black arrows), which was felt to be a continuation of the pathologic enhancement noted in the brainstem. Coronal post contrast T1-weighted MR image (H) of the brain from an MRI done 5 months earlier showed a small nodular area of enhancement within the pons (black arrowhead).

levels were normal. After excluding the different possibilities for the brainstem findings and given the typical clinical and the characteristic radiological findings, the clinical diagnosis

of CLIPPERS was considered. The cause of the basal ganglia infarcts was not exactly clear. These could have been related to his hypertension or drug abuse. However, given the small

punctate foci of nodular and linear enhancement similar to that seen in the brainstem, the primary consideration was progressive involvement of the perivascular disease process into the basal ganglia. The lacunar strokes could

have been caused by occlusion of the small lenticulostriate vessels by the lymphocytic process in the basal ganglia. The patient was started on a five-day course of high dose IV solumedrol. The patient demonstrated immediate improve-

Figure 2 MRI of the brain. Axial T1-weighted (A), post contrast T1-weighted (B), coronal post contrast T1-weighted (C) and axial Flair (D) MR images of the brain demonstrate multiple punctate nodular foci of ill-defined enhancement (small white arrows) involving the pons and bilateral middle cerebellar peduncles (post contrast images) with corresponding FLAIR signal hyperintensity (black arrow). No restricted diffusion was noted (not shown). Follow-up axial Flair (E) and post contrast T1-weighted (F) images demonstrate a decrease in the number of punctate and nodular enhancing lesions as well as diminished FLAIR signal hyperintensities in the brainstem.

ment in symptoms 48-72 hours after starting the IV solumedrol and was discharged home on a tapered dose of oral prednisone.

Case 2: A 56-year-old woman presented with progressive ataxia, dysarthria and dysphagia.

Abnormal tone was noted in both extremities with slow fine finger movements bilaterally (R<L). Coordination was grossly abnormal and wide-based ataxic gait was noted consistent with cerebellar dysfunction. MRI of the brain

demonstrated multiple punctate nodular foci of ill-defined enhancement involving the pons and both middle cerebellar peduncles with minimal corresponding FLAIR signal hyperintensity (Figure 2). No restricted diffusion was noted. Lumbar puncture was negative. All blood tests were negative. MRI of the cervical and thoracic spine was negative except for mild degenerative disease in the cervical spine. Based on the clinical picture and the radiological findings, the possibility of CLIPPERS was considered and the patient was started on an oral five-day course of prednisone. Following steroid therapy, the patient demonstrated some improvement in her clinical symptoms. This correlated with the imaging findings, which demonstrated minimal improvement in the foci of enhancement as well. She returned in three months with what appeared to be a relapse of her signs and symptoms. She was then started on a course of rituximab and dexamethasone with some resolution of her signs and symptoms.

Discussion

CLIPPERS is a recently described disease entity, whose pathogenesis is still not clearly understood^{6,9}. Earlier reports suggested an autoimmune etiology based on the presence of a perivascular and parenchymal T-lymphocyte cell infiltrate in brainstem biopsies of suspected cases, combined with a clinical response to immunosuppressive steroid therapy, with the target autoantigen likely being in the perivascular regions of the brainstem^{6,9}. Despite its responsiveness to steroids, CLIPPERS cannot be considered a benign entity since recent reports noted have lymphoma associated with it^{1,8}. More recently, questions have been raised as to whether CLIPPERS actually represents a new disease entity or is a syndrome including different overlapping diseases and their prestages⁴.

Clinical findings are due to the involvement of the brainstem and most commonly include ataxia and diplopia⁶. Other less common presentations include dysarthria and an altered sensation of the face and the scalp. Non-specific symptoms such as dizziness, nausea, dysgeusia, tinnitus, nystagmus, parasthesias, sensory loss and spasticity have also been reported⁶.

The imaging findings of this disease entity are striking and a hallmark of the disease process. MRI demonstrates multiple punctate and linear foci of enhancement involving the brainstem and adjacent structures⁶. The en-

hancing lesions have a radiating pattern and lesions are typically smaller and less numerous when they are located in areas other than the pons. No significant mass effect is noted. The basal ganglia, cerebellum, corpus callosum and the spinal cord may also be involved^{6,7,9}. The parenchyma of the involved areas demonstrates ill-defined T2/FLAIR signal hyperintensity suggesting edema. In one of our cases, characteristic punctate nodular enhancement was noted, not only involving the brainstem, but also the basal ganglia (case 1). Along with the characteristic enhancement pattern, a few foci of restricted diffusion were also noted in the basal ganglia, consistent with lacunar infarcts. As the patient had not been on any steroid therapy for six months since his original presentation, it is conceivable that the primary perivascular process involving the brainstem extended into the perivascular spaces in the basal ganglia. The small lacunar infarcts could have been caused by the perivascular exudates occluding the lenticulostriate vessels traversing the basal ganglia. After the diagnosis of CLIPPERS was made, prompt therapy with IV steroids was instituted resulting in an immediate improvement of symptoms.

Some authors have suggested that the characteristic clinical features and the imaging findings may preclude the need for a biopsy⁶. Prompt recognition and treatment of the disease is important since irreversible neuronal damage may occur². Prompt therapy with an intravenous course of high dose IV steroids followed by a tapering course of oral steroids has been recommended⁹. Relapses are common and a prolonged course of steroids may be needed in some cases⁹. Other immunosuppressive agents such as methotrexate and cyclophosphamide have also been given as maintenance therapy to prevent relapses and the long-term side-effects of corticosteroids^{3,6,7}. Treatment with steroids usually results in prompt improvement and sometimes a resolution of clinical symptoms. Clinical improvement is paralleled by improvement in the areas of enhancement and signal abnormality (Figure 2). Brain biopsy is the only way to establish a definite diagnosis and might be warranted when a patient with suspected CLIPPERS fails to respond to steroids, in order to exclude an alternative diagnosis such as lymphoma⁵.

CSF analysis is usually not specific. Positive findings include protein elevation, elevated lymphocytic count and elevated oligoclonal bands in some cases^{6,9}.

Differential diagnosis should include all entities with localized brainstem involvement such as neurosarcoidosis, CNS lymphoma, lymphomatoid granulomatosis, CNS vasculitis, brainstem encephalitis and chronic perivascular infectious processes such as tuberculosis, neurosyphilis, Whipple's disease and parasitic infection^{2,6}.

In conclusion, we described two cases of a rare disease entity called CLIPPERS. One of the cases demonstrated an additional finding

of lacunar infarcts in the basal ganglia with associated underlying nodular enhancement, which we feel, might be related to the spread of the perivascular disease process from the brainstem. As more and more cases are reported and while pathogenesis of this disease entity continues to evolve, it is important to understand that CLIPPERS is not a benign entity and prompt diagnosis and treatment are needed to prevent future complications and relapses.

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