CASE REPORT

A Case of Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) in East Asia

Rie Tohge, Masahiro Nagao, Akira Yagishita and Shiro Matsubara

Abstract

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) syndrome is a clinically and radiologically distinct pontine-predominant perivascular neuroinflammation showing T lymphocyte infiltration. It is assumed to have an autoimmune or other inflammatory mediated pathogenesis. We report the first known case of CLIPPERS in East Asia, characterized by multiple punctate enhancement of the brainstem extending to the bilateral posterior limb of the internal capsule and caudal to the spinal cord conus. The patient had elevated IgE levels and a history of allergies, suggesting that lesions may arise from neuroinflammation in response to T lymphocyte infiltration into perivascular spaces.

Key words: CLIPPERS, brainstem, spinal cord, neuroinflammation, IgE

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Introduction

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) syndrome was recently described by Pittock and colleagues in 2010 in six American and two European patients (1). It bears the radiological and pathological features of a treatable, brainstem-predominant, and clinical entity characterized by punctate enhancement throughout the pons on brain magnetic resonance imaging (MRI) and a perivascular-predominant infiltrate of T lymphocytes in the white matter without demyelination on neuropathological examination. Patients present with cranial nerve symptoms, such as diplopia, dysarthria, nystagmus, and cerebellar ataxia. The pathogenic mechanism of CLIPPERS is unknown although neuropathological findings and the clinical response to immunosuppressants suggest an autoimmune or other inflammatory mediated pathogenesis (1). We report the first known CLIPPERS case in East Asia, a female patient presenting with the typical punctate enhancement of the brainstem that also extended to the bilateral posterior limbs of the internal capsule and throughout the spinal cord.

Case Report

A 54-year-old woman with temporal diplopia and distal dominant paresthesia of the extremities experienced worsening symptoms over two months before admission. She also suffered from mild gait disturbances with spasticity and nocturnal leg cramps. Her past medical history included polymyalgia rheumatica for the past two years, which was effectively treated using oral prednisolone. On neurological examination, horizontal gaze nystagmus was observed. There was no oculomotor disturbance or other cranial nerve abnormalities. Tendon reflexes in the arms and legs were brisk. Bilateral pathological reflexes were positive. Distal dominant paresthesia of the extremities was observed. Vibratory sense was decreased in both legs but there was no position sense deficit. Her limb muscle strength, coordination, cognitive functions, and other neurological functions were normal.

Brain magnetic resonance imaging (MRI) revealed a characteristic pattern of punctate enhancement extending from the brainstem to the bilateral posterior limbs of the internal capsule (Fig. 1A, B) that appeared as patchy lesions in the bilateral posterior limbs of the internal capsule and left cere-
abnormal signs. Mography and gallium-67 scintigraphy did not reveal any nating mononeuropathy multiplex. Truncal computed to- (right: 37.7 m/s, left: 36.7 m/s; Table 1), indicating demyeli-
duction block or temporal dispersion in both tibial nerves indicated slightly reduced conduction velocity without con-
vealed no malignant cells. A nerve conduction study (NCS) revealed no oligoclonal bands. Cytological analysis re-
protein. Myelin basic protein was normal (<4 ng/mL) and well as scattered punctate gadolinium (Gd) enhancement
dulla to the conus on T2-weighted images (Fig. 2A, B) as intensity lesions without swelling extending from the me-
bral peduncle on diffusion-weighted images (small arrows) (C, D) and T2-
Figure 1. Initial brain magnetic resonance image (MRI) from August 2011 showing multiple, small high-intensity lesions on FLAIR images (arrowheads) (A) and punctate enhancement lesions along the brainstem (arrowheads) (B). Patchy lesions in the bilateral posterior limb of the internal capsule and left cerebral peduncle on diffusion-weighted images (small arrows) (C, D) and T2-weighted images (arrows) (E, F).

Laboratory investigations revealed elevated serum IgE lev-
als (375 IU/mL; normal <170 IU/mL) and seropositive status for a specific IgE to cedar pollen. Antithyroid peroxi-
dase (TPO) antibody was also elevated (467.8 IU/mL; nor-
mal <16 IU/mL) although the patient was euthyroid as re-
vealed by thyroid ultrasonography. The patient was sero-
negative for antinuclear antibody, rheumatoid factor, anti-SS-
A and anti-SS-B antibodies, anti-RNP antibody, perinuclear antineutrophil cytoplasmic antibody, cytoplasmic antineutro-
phil cytoplasmic antibody, anti-Sm antibody, anti-aquaporin 4 antibody, and anti-ganglioside antibody. Serum vitamin B12, folic acid, angiotensin-converting enzyme, rizothyme, and soluble interleukin-2 receptor were within normal ranges. The HLA typing was A11, A24, B62, and B52. Cerebrospinal fluid analysis revealed pleocytosis (67 white blood cells per mm³, 99% lymphocytes) and 84 mg/mL total protein. Myelin basic protein was normal (<4 ng/mL) and there were no oligoclonal bands. Cytological analysis re-
vealed no malignant cells. A nerve conduction study (NCS) indicated slightly reduced conduction velocity without con-
duction block or temporal dispersion in both tibial nerves (right: 37.7 m/s, left: 36.7 m/s; Table 1), indicating demyeli-
nating mononeuropathy multiplex. Truncal computed to-
mography and gallium-67 scintigraphy did not reveal any abnormal signs.

After intravenous methylprednisolone treatment (1,000 mg daily for the first 3 days) and oral prednisolone (1 mg/kg daily), the patient’s symptoms improved but with persistent paresthesia of the extremities. A follow-up MRI two months later revealed no remaining punctate Gd-enhancing lesions in the brainstem or spinal cord (Fig. 3A-C). Follow-up NCS indicated chronically reduced conduction velocity in the tib-
ial nerves (not shown). The patient is currently on tapering doses of prednisolone (5 mg less each month) and has re-
ained free of reemergence and exacerbation of symptoms.

**Discussion**

The present case was diagnosed as CLIPPERS based on the clinical and radiological findings, and is to our knowl-
edge the first reported case in East Asia. The patient suf-
f ered from transient diplopia, which disappeared within two weeks along with horizontal gaze nystagmus and myel-
pathic disorders such as paresthesia and hyperreflexia of the extremities, pathological reflexes, and a decreased sense of vibration in both lower limbs, that intensified over two months before admission. In previously described cases, oculomotor disturbances (transient or continuous) and ataxia almost always appear at onset. Radiology consistently re-
veals lesions of the brainstem, and some patients present with lesions extending down to the cervical and thoracic spina-
lar cord and rostral to the cerebellar peduncle and hemi-
sphere, thalamus, basal ganglia, corpus callosum, and sub-
cortical white matter (1-3). The MRI of the present patient revealed a characteristic pattern of punctate enhancement ex-
tending from the brainstem to the bilateral posterior limbs of the internal capsule and spinal cord. These lesions promptly disappeared with corticosteroid monotherapy, whereas rapid glucocorticosteroid tapering led to reemergence of clinical
A majority of these patients (74%) presented with myelitis in the cervical cord, but it rarely extended over the entire spinal cord or appeared as punctate enhancement in the pons. In addition, while pathological findings in atopic myelitis reveal vasculitis infiltrated by eosinophilia, CLIPPERS cases exhibit T lymphocytic infiltrations (1-3, 6). Atopy, a pathological condition that presents with elevated IgE levels in response to various environmental antigens, including mite and cedar pollen, typically includes atopic dermatitis, allergic rhinitis, and bronchial asthma. These three conditions are type I (immediate) allergy. However, all of the pathophysiological conditions of atopic dermatitis cannot be explained by type I allergy. Pathological findings from atopic dermatitis patients reveal T lymphocytic infiltrate in intraepidermal lesions that resemble allergic contact dermatitis resulting from type IV (late) allergy (7). Although most patients with atopic disease do not suffer from CLIPPERS, it has been suggested that elevated IgE and T lymphocytic infiltrate within the perivascular spaces in CLIPPERS patients may be caused by immediate and late allergic reaction similar to atopic dermatitis. During the immediate allergic reaction, antigen-specific IgE is produced. In the late allergy phase, macrophages responding to the antigen may stimulate helper T lymphocytes. A sensitized T-lymphocyte-specific response may lead to cell-mediated immunity with concomitant release of cytokines and ensuing perivascular inflammation.

In addition, anti-TPO antibody, which is frequently elevated in Hashimoto’s disease, was increased in the present patient, but thyroid ultrasonography did not reveal any abnormal signs. The characteristic pattern of punctate gadolinium enhancement on MRIs observed in CLIPPERS patients is not observed in Hashimoto’s disease. Nonetheless the association between anti-TPO antibodies and CLIPPERS warrants further investigation because the presence of anti-TPO antibodies often indicates an autoimmune process.

Another distinct finding in the present patient was subclinical peripheral neuropathy with demyelination, as evidenced by reduced conduction velocities in the tibial nerves that persisted even after successful steroid therapy. The cause of this neuropathy could not be identified on examination. Demyelination was not observed in the central lesion associated with CLIPPERS. Although peripheral neuropathy may be encountered with diseases other than CLIPPERS, it is also possible that CLIPPERS can cause functional impairment in both the central and peripheral nervous systems, which may have different pathological mechanisms, and that the therapeutic responses of CLIPPERS-related lesions to steroids may differ between the peripheral nerves and the brainstem or spinal cord. Alternatively, reduced tibial nerve conduction velocities may be improved by higher doses of glucocorticosteroids. Both future case reports and long-term follow-up examinations of pre-existing CLIPPERS cases should investigate whether peripheral neuropathy is involved in other CLIPPERS cases and if these cases share unique clinical symptoms or a common etiology.

There are still only a few reported cases of CLIPPERS, features and radiological lesions. A diagnosis of CLIPPERS requires exclusion of other diseases that present with similar lesions such as neuromyelitis optica, neurosarcoïdosis, neuro-Behçet’s disease, central nervous system vasculitis, and malignant lymphoma. Although these disorders were excluded on examination, high serum IgE levels and positive status for Cryptomeria-specific IgE were observed. The patient had a 20-year history of seasonal allergic rhinitis in the spring. Kastrup et al. reported that two of three cases with CLIPPERS exhibited elevated IgE levels at some point during the clinical course (2). Kira et al. described a distinct neuroinflammatory disease, atopic myelitis, characterized by acute localized myelitis with elevated IgE levels specific to the mite antigen (4, 5). A majority of these patients (74%)
which has hampered investigations into the pathogenic mechanisms of this disease. Although only three cases with CLIPPERS have shown IgE elevation, we stress the importance of serum IgE measurements in suspected cases and the need for further clinical investigations on the relationship between elevated IgE levels and CLIPPERS. Long-term follow-up of each case presented to date could lead to a deeper understanding of the pathological processes and clinical manifestations of CLIPPERS, resulting in better treatment and disease prognosis.

The authors state that they have no Conflict of Interest (COI).

References


Table 1. Nerve Conduction Study on Admission

<table>
<thead>
<tr>
<th>Motor</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>DL (ms) distal O/Pfast MCV (m/s)</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Lt. Median N.</td>
<td>3.1 8.4 48.7 - -</td>
</tr>
<tr>
<td>Lt. Ulnar N.</td>
<td>3.1 6.9 57.1 - -</td>
</tr>
<tr>
<td>Lt. Tibial N.</td>
<td>3.7 11.8 36.7 - -</td>
</tr>
<tr>
<td>Lt. Sural N.</td>
<td>2.8 10.1 51.6 - -</td>
</tr>
<tr>
<td>Rt. Median N.</td>
<td>2.4 7.3 64.3 - -</td>
</tr>
<tr>
<td>Rt. Ulnar N.</td>
<td>3.2 13.7 37.7 - -</td>
</tr>
</tbody>
</table>

Normal range* (>50years old)

<p>| Motor     | Sensory            |
|-----------|-------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>DL (ms) distal O/Pfast MCV (m/s)</th>
<th>CB TD F-Latency (ms) F-Occurr. (%) F-WVCV (m/s)</th>
<th>DL (ms) distal O/Pfast SCV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median N.</td>
<td>&lt;3.7 &gt;5.5 &gt;52.2 &lt;3.1 &gt;12.9 &gt;48.1</td>
<td>- - - - -</td>
<td>- - - - -</td>
</tr>
<tr>
<td>Ulnar N.</td>
<td>&lt;2.5 &gt;6.8 &gt;51.3 &lt;2.5 &gt;7.7 &gt;47.1</td>
<td>- - - - -</td>
<td>- - - - -</td>
</tr>
<tr>
<td>Tibial N.</td>
<td>&lt;3.8 &gt;8.8 &gt;45.1</td>
<td>- - - - -</td>
<td>- - - - -</td>
</tr>
<tr>
<td>Sural N.</td>
<td>&lt;2.5 &gt;6.3 &gt;43.9</td>
<td>- - - - -</td>
<td>- - - - -</td>
</tr>
</tbody>
</table>

Bandpath = 5 to 5 kHz, N = nerve, DL = distal latency, O/P = onset-to-peak, MCV = motor nerve conduction velocity, CB = conduction block, TD = temporal dispersion, F-Occurr. = F-Occurrence, F-WVCV = F-wave conduction velocity, SCV = sensory nerve conduction velocity

* normal control data of our hospital

Figure 3. After initial treatment with intravenous methylprednisolone and daily oral prednisolone, a follow-up magnetic resonance image (MRI) from October 2011 revealed the disappearance of the punctate gadolinium (Gd) enhancing lesions in the brainstem and spinal cord (A, B, C).
responsive to steroids with initial normal magnetic resonance imaging. Brain 134: e184, 2011.


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