

[ CASE REPORT ]

## Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) with Limbic Encephalitis

Yasuyuki Ohta, Emi Nomura, Keiichiro Tsunoda, Toru Yamashita, Yoshiaki Takahashi, Kota Sato, Mami Takemoto, Nozomi Hishikawa and Koji Abe

### Abstract:

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory central nervous system disorder that mainly involves in the brainstem, basal ganglia and cerebellum. We herein report the case of a patient with CLIPPERS, which was diagnosed based on the clinical and radiological features. After initially responded to steroid treatment, the patient developed limbic encephalitis. The patient presented with memory disturbance, a delirious state and emotional incontinence. A cerebrospinal fluid study revealed interleukin-6 elevation and enhanced bilateral hippocampal lesions were observed on MRI. The patient was successfully treated with methylprednisolone pulse therapy. This is the first case of CLIPPERS with limbic encephalitis involving the bilateral hippocampus.

**Key words:** CLIPPERS, hippocampus, IL-6, limbic encephalitis, meningoencephalitis, MRI

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### Introduction

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory central nervous system (CNS) disorder that mainly involves in the brainstem, basal ganglia, cerebellum and spinal cord, with T lymphocyte infiltration (1, 2). The clinical characteristics of CLIPPERS emerge from CNS lesions, and usually include oculomotor abnormalities, facial palsy, dysarthria, paraparesis and ataxia (1-4). Limbic encephalitis with hippocampal lesions has not previously been reported in CLIPPERS. We herein report the first case of CLIPPERS with bilateral limbic encephalitis in a patient who presented with memory disturbance and a delirious state. The patient's condition was successfully treated with methylprednisolone pulse therapy.

### Case Report

A 37-year-old woman was admitted to our hospital with

progressive numbness and muscle weakness on the left side of her face, and left upper and lower extremities, which had persisted for 9 days, and vertigo, which had persisted for 6 days. A neurological examination revealed vertical and lateral gaze limitation, nystagmus in the bilateral eyes, dysarthria and dysphagia. She showed hyperreflexia in all extremities, and left Hoffmann, Babinski and Chaddock reflexes were all positive. She showed marked truncal and mild limb ataxia. Hypoesthesia was observed in the left upper and lower extremities and left trunk. Her mini-mental state examination (MMSE) score (30/30), Hasegawa dementia score-revised (HDS-R; 30/30), frontal assessment battery (FAB) score (18/18) and Montreal cognitive assessment (MoCA) score (27/30) showed normal cognitive and frontal cerebral functions (Table). Her geriatric depression scale (GDS) score (6/15) suggested a depressive state, but the apathy scale (AS; 16/42) and Abe's Behavioral and Psychological Symptoms of Dementia (ABS) score (0/44) (5) were normal.

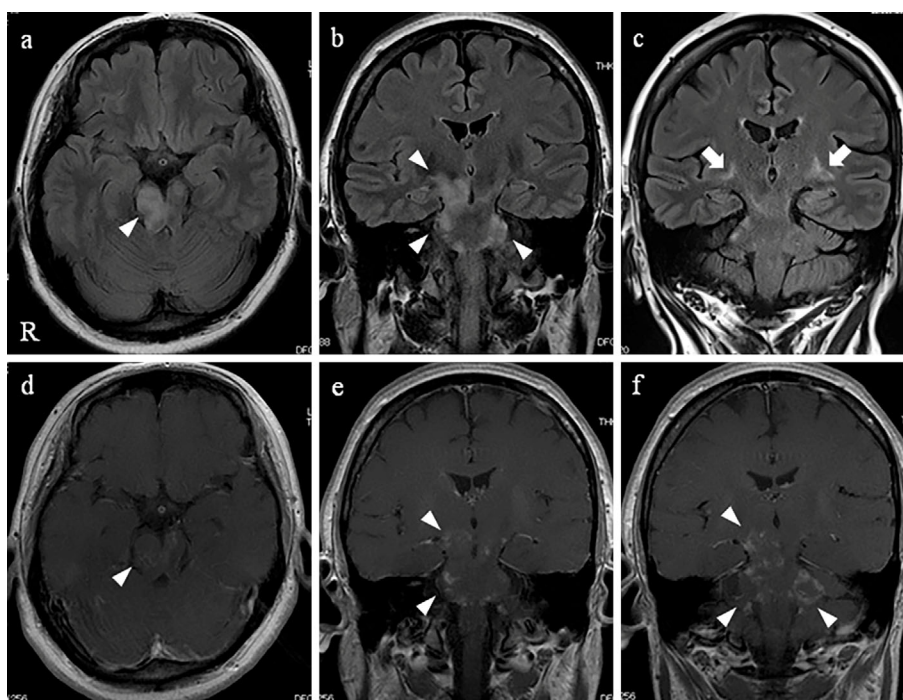
Magnetic resonance imaging (MRI) revealed high intensity spots in the midbrain, pons, bilateral middle cerebellar

**Table 1. Cognitive Functions and CSF Parameters.**

			1st admission	2nd admission	
		(Normal range)		Before treatment	After treatment
Cognitive function	MMSE		30	23	29
	HDS-R		30	22	28
	FAB		18	14	18
	MoCA		27	21	26
Affective function	GDS		6	9	6
	AS		16	16	14
	ABS		0	0	0
Serum	SIL2R	(122 - 496 U/mL)	245	249	ne
	AQP4	(0 - 5 U/mL)	<1.3	1.6	ne
CSF	Cell	(0 - 5 / $\mu$ L)	11	12	4
	Pro	(10 - 40 mg/dL)	54	70	63
	MBP	(0 - 102 pg/mL)	67.4	144	ne
	IL-6	(0 - 4 pg/mL)	119	96.8	3.3
	OCB		+	+	ne

ne: not examined

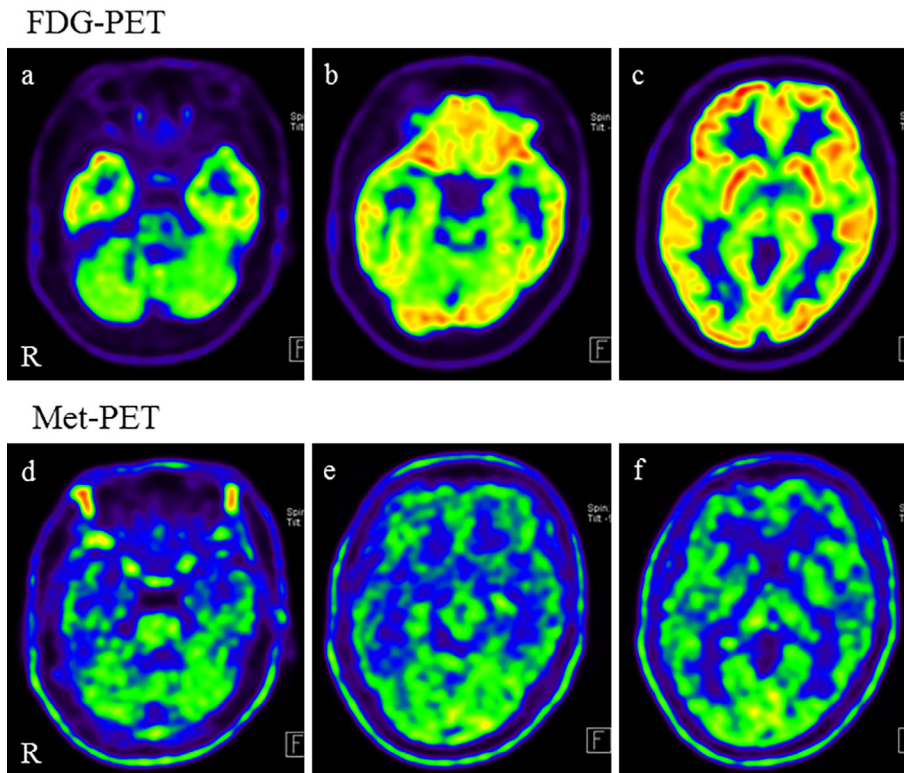
MMSE: mini-mental state examination, HDS-R: Hasegawa dementia score-revised, FAB: frontal assessment battery, MoCA: Montreal cognitive assessment, GDS: geriatric depression scale, AS: apathy scale, ABS: Abe's behavioral and psychological symptoms of dementia, SIL2R: soluble IL-2 receptor, AQP-4: anti-aquaporin 4, Pro: protein, MBP: myelin basic protein, IL-6: interleukin-6, OCB: oligoclonal bands



**Figure 1.** Brain magnetic resonance image (MRI) on the first admission. Fluid-attenuated inversion recovery (FLAIR) MRI showed hyperintense lesions in the midbrain (a, arrowhead), pons, bilateral middle cerebellar peduncles, thalamus (b, arrowheads) and basal ganglia (c, arrows). Numerous punctuate and curvilinear enhanced lesions were also observed in the same lesions on T1-weighted imaging (WI) (d-f, arrowheads).

peduncles, thalamus and basal ganglia on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 1a-c, Supplementary material Fig. 1a, b, arrowheads, arrows) with numerous punctuate and curvilinear enhancements (Fig. 1d-f, arrowheads). Magnetic resonance angiogra-

phy revealed normal findings. Spine MRI revealed no cervical, thoracic or lumbar cord lesions. All laboratory and cerebrospinal fluid (CSF) analyses to detect infection, malignancy, sarcoidosis, collagen disease and neuromyelitis optica were negative or normal-as were tests for antibodies



**Figure 2.** Representative brain fluorodeoxyglucose-position emission tomography ( $^{18}\text{F}$ -FDG-PET; a-c) and methionine PET ( $^{11}\text{C}$ -Met-PET; d-f) images, suggesting the absence of malignant lesions.

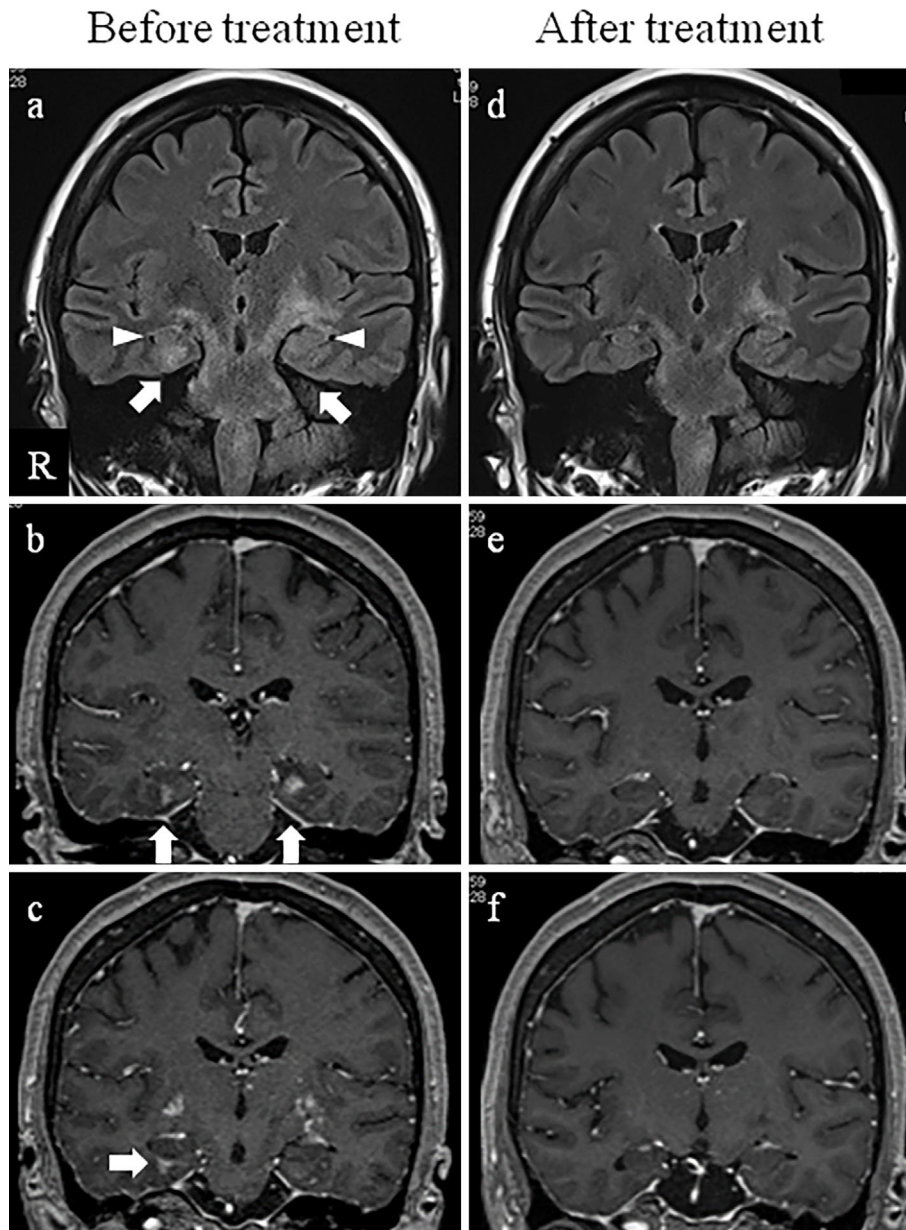
for parasites, antigens for fungi, a polymerase chain reaction (PCR) for tuberculosis, tumor markers and soluble interleukin (IL)-2 receptor (SIL2R), autoantibodies with anti-ganglioside and anti-glutamate receptor antibodies, angiotensin-converting enzyme (ACE), and anti-aquaporin 4 (AQP-4) antibodies. The patient's human leukocyte antigen type was A11, A33, B67 and B44. A CSF analysis revealed that the patient's level of myelin basic protein (MBP) was normal (67.4 pg/mL), while her IL-6 level was markedly elevated (119.0 pg/mL) (Table). The CSF cytology was class II. The patient was positive for oligoclonal bands (OCB). Whole body computed tomography, fluorodeoxyglucose-position emission tomography (PET) and methionine PET suggested no inflammatory or malignant lesions in the whole body, including the brain (Fig. 2). The suspected diagnosis was CLIPPERS. All of her symptoms showed a marked improvement following two courses of methylprednisolone pulse therapy (1 g daily for 3 days). She was discharged without additional oral prednisolone at 10 days after the steroid treatment.

However, 3 weeks after discharge, she began to show progressive symptoms with headache, nausea, double vision, numbness of the left face and memory disturbance, and was thus admitted again at 30 days after the initial discharge. On the second admission, left extra oculomotor muscle disturbance, muscle weakness and sensory disturbance of the left face and left upper and lower extremities were observed. Her deep tendon reflexes still displayed hyperreflexia in all extremities without pathological reflexes. She developed

marked truncal ataxia again. Her MMSE and HDS-R scores decreased to 23/30 and 22/30, and she showed immediate and recent memory disturbance (Table). Her FAB and MoCA scores also decreased to 14/18 and 21/30, respectively. Her GDS score worsened to 9/15; however, her AS score and ABS were the same as at the first admission (16/42 and 0/44, respectively). She also showed delirium and emotional incontinence.

MRI at the second admission revealed high intensity spots in the midbrain, pons and bilateral middle cerebellar peduncles and thalamus, as well as in bilateral hippocampus and parahippocampal gyrus on a T2-weighted and FLAIR images (Fig. 3a, arrowheads, arrows) with enhancement in the bilateral hippocampus and parahippocampal gyrus on T1-weighted imaging (Fig. 3b, c, arrows). Magnetic resonance spectroscopy (MRS) of the dorsal hippocampus showed bilateral increases of choline (Cho) peaks (Fig. 4, arrowheads) with normal levels of N-acetyl acetate (NAA) peaks (Fig. 4, arrows), suggesting demyelination or necrosis, but not a tumor. All of the laboratory and CSF measurements for malignancy and sarcoidosis including tumor markers with SIL2R, ACE or anti-glutamate receptor antibodies were again either negative or normal. At the second admission, the patient's CSF cytology was class II and had not changed. A CSF analysis, revealed MBP and IL-6 elevation (144.0 pg/mL and 96.8 pg/mL, respectively), the patient was still positive for OCB (Table).

The patient's immediate and recent memory disturbance and psychiatric symptoms were attributable to limbic en-

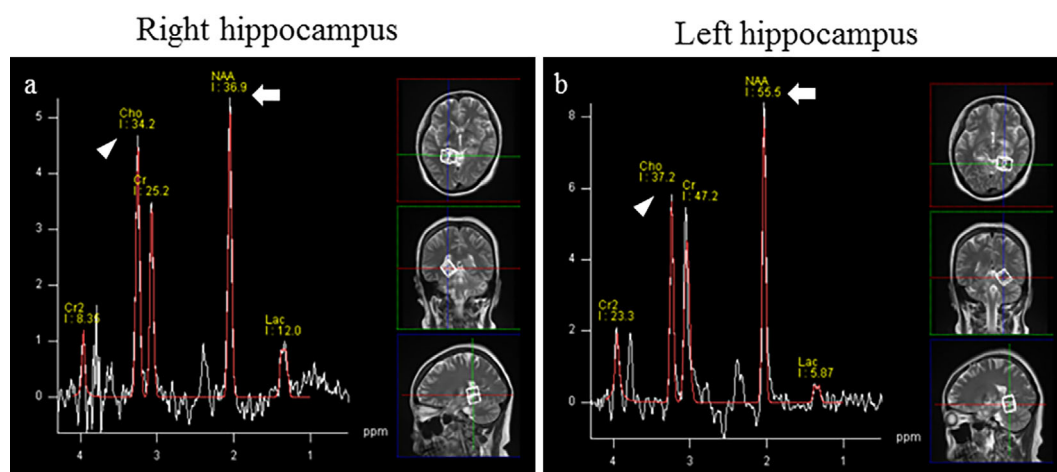


**Figure 3.** Brain magnetic resonance image (MRI) on the second admission, when the patient presented with memory disturbance and a delirious state. Fluid-attenuated inversion recovery (FLAIR) MRI showed new hyperintense lesions in the bilateral hippocampus (a, arrowheads) and parahippocampal gyrus (a, arrows) with enhancement on T1-WI (b, c, arrows). After treatment with three courses of methylprednisolone pulse therapy, the bilateral hippocampal and parahippocampal gyrus lesions showed marked improvements (d) with the disappearance of enhancement (e, f).

cephalitis affecting the bilateral hippocampus, which was closely associated with CLIPPERS. After treatment with three courses of methylprednisolone pulse therapy, followed by oral prednisolone (60 mg per day), all of the patient's symptoms subsided, including the memory disturbance and psychiatric symptoms, and her cognitive function improved to the normal range (Table). The patient's pleocytosis, CSF level of IL-6, and the multiple lesions with enhancement on brain MRI, also greatly improved (Table, Fig. 3d-f). The oral prednisolone dosage was tapered without recurrence.

## Discussion

CLIPPERS is primarily diagnosed based on the clinical and radiological features (1, 4). Clinically, CLIPPERS is characterized by subacute symptomatology related to the brainstem, cranial nerve or cerebellar involvement. In patients with CLIPPERS, MRI shows characteristic lesion patterns including numerous punctate or nodular enhancing 'peppering' lesions in the pons, with or without lesions in the brachium pontis or cerebellum. On our patient's first admission, CLIPPERS was suspected based on the clinical and



**Figure 4.** Representative magnetic resonance spectroscopy (MRS) images of the dorsal hippocampus. MRS showed bilateral increases of choline (Cho) peaks (a, b, arrowheads) with normal N-acetyl acetate (NAA) peaks (a, b, arrows), suggesting demyelination or necrosis, but not tumors.

neurological findings (Fig. 1). Serum, CSF and FDG and Met-PET (Fig. 2) studies excluded other neurological diseases. OCB is often observed in CLIPPERS (1). Although the patient was not examined for antibodies to myelin-oligodendrocyte glycoprotein (MOG), a CLIPPERS patient with longitudinally extensive transverse myelitis was reported to have antibodies to MOG, suggesting that CLIPPERS is a syndrome rather than a distinct disease (6). The clinical symptoms and multiple enhanced lesions observed on MRI in the present case improved after methylprednisolone pulse therapy, which was compatible with a diagnosis of CLIPPERS (1, 4). The CSF IL-6 level is elevated in a number of CNS disorders (7), but has never been reported in CLIPPERS. Our patient showed marked CSF IL-6 elevation, which improved after methylprednisolone pulse therapy, suggesting that the CSF IL-6 level could become a new biomarker of disease activity in CLIPPERS.

Cognitive dysfunction, including dysexecutive syndrome and amnesic deficits, are found in some patients with CLIPPERS (3, 4). However, limbic encephalitis combined with hippocampal and parahippocampal gyrus lesions has never been reported in CLIPPERS (8). On the patient's second admission, she presented with immediate and recent memory disturbance and psychiatric symptoms, which were accompanied by enhanced intensity of the bilateral hippocampus and parahippocampal gyrus on MRI. These findings improved following methylprednisolone pulse therapy (Fig. 3). On MRI, the lesions of the midbrain, pons, thalamus, bilateral hippocampus and parahippocampal gyrus were connected, suggesting that the brainstem lesions might progress to thalamus, hippocampus and parahippocampal gyrus. Based on the serum, CSF and MRS findings, we considered that the limbic encephalitis in this patient was associated with CLIPPERS (Fig. 4). The results of these analyses did not support the diagnosis of other neurological disorders. Our case suggests that limbic encephalitis with CLIPPERS responds well to high-dose steroid therapy.

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

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