

Horizontal eyeball akinesia as an initial manifestation of CLIPPERS

Case report and review of literature

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Abstract

Background: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare chronic inflammatory disorder in the central nervous system (CNS), which is characterized by magnetic resonance imaging (MRI) appearance with punctate and curvilinear gadolinium enhancement “peppering” the pons. Lesions of CLIPPERS mainly involve the pons and the cerebellum. Adjacent structures such as the medulla and the midbrain may also be involved. It is proposed that CLIPPERS is an immune-mediated inflammatory condition characteristic of T-cell-predominant infiltrates and good responsiveness to corticosteroids.

Methods and Results: We report a 46-year-old woman who presented with horizontal eyeball akinesia and gait ataxia with characteristic MRI features of CLIPPERS. The possible pathogenesis, clinical manifestations, imaging features, treatment, and prognosis of this peculiar disorder are summarized.

Conclusion: This report contributes to the clinical understanding of CLIPPERS which may present with horizontal eyeball akinesia as an initial manifestation. The characteristic presentation of a subacute cerebellar and brainstem syndrome and pepper-like gadolinium enhancement was confirmed in this report. Long-term immunosuppressive treatment seems to be mandatory to sustain improvement. Azathioprine alone may be capable of maintaining remission.

Abbreviations: ADEM = acute disseminated encephalomyelitis, BBE = Bickerstaff brainstem encephalitis, CEA = carcino-embryonic antigen, CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, MS = multiple sclerosis, NMO = neuromyelitis optica, PACNS = primary angiitis of the central nervous system, PCNSL = primary central nervous system lymphoma.

Keywords: Brainstem, CLIPPERS, Corticosteroids, Neuroinflammation, Perivascular infiltration

1. Introduction

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) was first described in 2010 by Pittock et al^[1] as a unique form of brainstem encephalitis centered on the pons. However, the causes and the pathogenesis of CLIPPERS remain poorly understood thus far. The cardinal symptoms at onset include diplopia, gait ataxia, and facial paresthesia. Nystagmus, dysarthria, dysphagia, and other symptoms can also appear when disease progresses. Magnetic resonance imaging (MRI) may disclose characteristic

punctate and curvilinear gadolinium enhancement in a “pepper-like appearance” in the pons, midbrain, and cerebellum. Biopsy findings showed perivascular lymphohistocytic infiltrates with a T-lymphocyte predominance. Another major feature of CLIPPERS is clinical and radiological responsiveness to glucocorticosteroids (GCS), and withdrawal of GCS may result in relapses of CLIPPERS.^[1–3] Due to the lack of specific biomarkers, it remains a debated issue whether CLIPPERS is an independent new disorder. We herein report a new case and summarize the up-to-date knowledge of the possible pathogenesis, clinical manifestations, and radiological features, as well as treatment modalities and prognosis of CLIPPERS based on 60 previously reported patients with CLIPPERS.

2. Case report

The reporting of the following case was approved by the ethics committee of the First Hospital of Jilin University, Changchun, China. Though written informed consent was not obtained, the patient’s information was anonymized and de-identified. A 46-year-old woman was referred to our hospital with complaints of inability to move her eyeballs horizontally. She also complained of dizziness and gait unsteadiness that progressed over a period of 4 months. Two months after the onset, the patient was treated with dexamethasone (10 mg × 7d, 7.5 mg × 2d, 5 mg × 3d, 2.5 mg × 3d) in the local hospital and gained some improvement in her clinical symptoms. Ten days before admission, her clinical symptoms deteriorated. Upon

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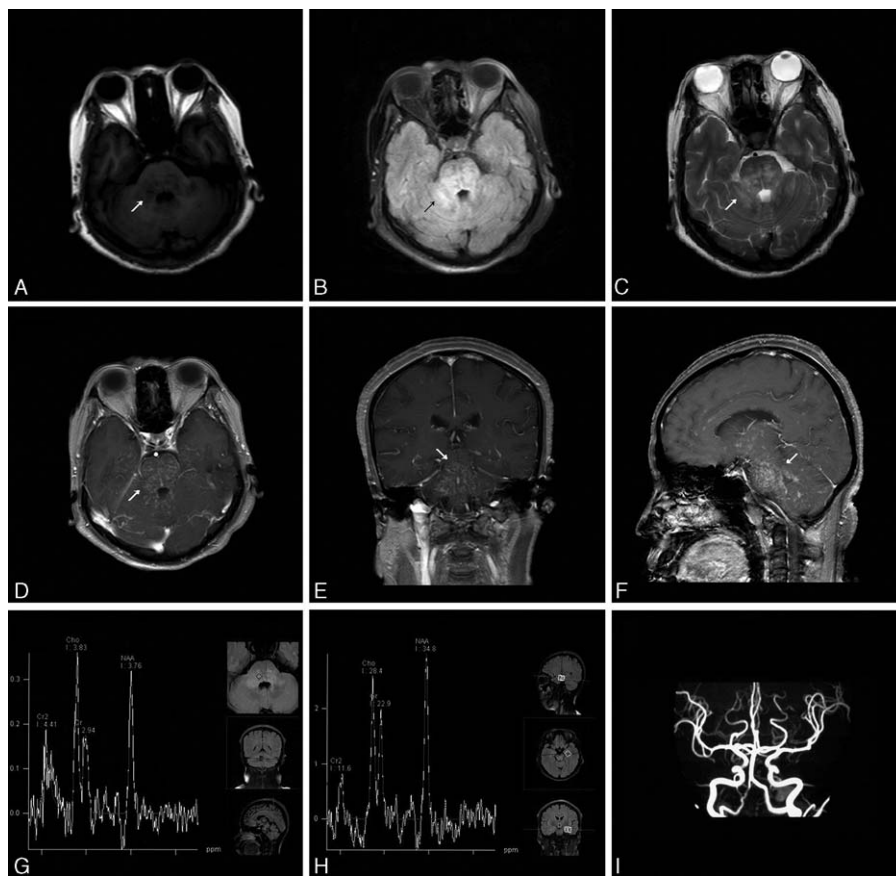


Figure 1. MRI reveals hypointensity on T1 images (A) and hyperintensity on T2 (C) and FLAIR images (B) localized in pons, mesencephalon, and cerebellum, with punctuate gadolinium enhancement in a “pepper-like appearance” centered on the pons in axial (D), coronal (E) and sagittal view (F). MRS (G–H) and MRA examinations (I) are normal. MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy.

neurological examination, cerebellar ataxia, dysarthria, decreased memory and calculation ability, left blepharoptosis, inability of eyeball movement in the horizontal direction and loss of positional sense, as well as mild dysmetria on bilateral finger-to-nose and heel-to-shin testing were noted. Vertical eye movement and ocular convergence were normal. The oculocephalic reflex, corneal reflex, pupillary light reflex, and accommodation reflex were also normal. No nystagmus or facial palsy was observed. No other cranial nerve abnormalities were noted. Limb muscle strength and tendon reflexes in the arms and legs were normal. The Babinski sign and the Chaddock sign were negative bilaterally. Four months after onset, an MRI examination revealed signal abnormalities localized in pons, mesencephalon, and cerebellum on the T1 weighted imaging (T1WI), T2 weighted imaging (T2WI), and fluid attenuated inversion recovery (FLAIR) images with punctuate gadolinium enhancement in a “pepper-like appearance” centered on the pons and without mass effect. The magnetic resonance angiography (MRA) and magnetic resonance spectroscopy (MRS) examinations were normal (Fig. 1). Chest computed tomography (CT) examination was normal. Cerebrospinal fluid (CSF) analysis demonstrated an elevated protein level (0.76 g/L, normal range: 0.15–0.45 g/L) and a normal amount of cells (4×10^6 cells/L; normal range: $0\text{--}8 \times 10^6$ cells/L). The levels of glucose and chlorides were normal. The permeability of the blood-brain barrier was increased (11.8×10^{-3} , normal range: $<5.0 \times 10^{-3}$). Blood tumor markers were all within the normal range, except for a slightly elevated level of carcino-embryonic antigen (CEA)

(5.75 ng/mL, normal range: <5.0 ng/mL). The patient was treated with methylprednisolone ($500 \text{ mg} \times 7\text{d}$, $250 \text{ mg} \times 7\text{d}$, $120 \text{ mg} \times 7\text{d}$) followed by tapering dose of oral steroids. Oral steroids treatment was started with 48 mg of methylprednisolone per day and was tapered to 20 mg of methylprednisolone per day, while azathioprine (100 mg/d) was administered as a corticosteroid sparing agent on the third month of the treatment scheme. Oral steroid (20 mg/d) lasted for 45 days and then was tapered and discontinued. We observed marked improvement of the clinical symptoms after the use of methylprednisolone. The symptoms of horizontal eyeball akinesia, dizziness, and gait unsteadiness completely resolved. Memory and calculation ability got much improved. Mild horizontal nystagmus was still notable. MRI showed resolution of gadolinium enhancement lesions after 4-month immunosuppressive therapy (Fig. 2). The patient was still on azathioprine treatment (100 mg/d). She has remained stable with mild impairment of memory and calculation ability but without other symptoms. No more relapses have been observed for 6 months after the treatment.

3. Discussion

The diagnostic criteria of CLIPPERS are yet to be determined. The diagnosis of CLIPPERS is made based on the clinical and neuroimaging findings and the exclusion of differential diagnoses. Subacute and progressive brainstem and cerebellar symptoms with characteristic MRI findings showing punctate enhancement in a “pepper-like appearance” centered on the pons are the

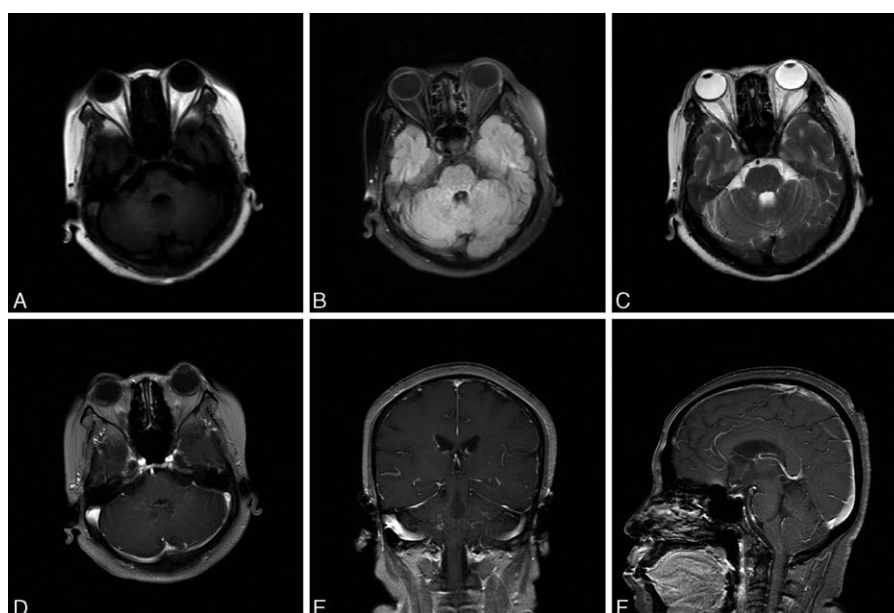


Figure 2. MRI shows resolution of lesions after 4-month immunosuppressive therapy on T1WI (A), T2WI (C), and FLAIR images (B). Axial (D), coronal (E), and sagittal (F) gadolinium-enhanced T1WI show decreased enhancement in the brainstem and the cerebellum. MRI = magnetic resonance imaging.

hallmarks of CLIPPERS syndrome.^[1] Our patient’s clinical and imaging manifestations were consistent with CLIPPERS. The diagnostic workup was negative for infections, autoimmune disorders, and paraneoplastic syndrome (Table 1). Bickerstaff brainstem encephalitis (BBE) was considered as a differential diagnosis. However, lesions of BBE are usually restricted to the brainstem, with thalamus and cerebellum spared. Besides, pepper-like gadolinium enhancement has not been reported in BBE. More importantly, a relapsing-remitting course of BBE is also rare.^[4] The MRS feature of primary central nervous system lymphoma (PCNSL) is a high Cho/NAA ratio. However, PCNSL cannot be completely excluded as patients with PCNSL may have atypical radiological presentations and may respond well to steroids. The differentiation between PCNSL and CLIPPERS is challenging. Taieb et al^[5] reported a case that developed a central nervous system B-cell lymphoma 2 years after initial diagnosis of CLIPPERS. They performed biopsy before they made the diagnosis of CLIPPERS. The biopsy in the case showed perivascular CD4-cell infiltrates, which matched with all

CLIPPERS findings. However, the patient was ultimately diagnosed as PCNSL. Subacute vascular lesion was excluded by the normal results of MRA. Central pontine myelinolysis was ruled out by the normal serum sodium level and relapsing-remitting course. Autoimmune encephalitis was also ruled out by the clinical and radiological findings, the typical topography of the lesions, and the negative results of the relevant antibodies, that is, anti-NMDA receptor, anti-AMPA1 receptor, anti-AMPA2 receptor, anti-CASPR2, anti-LGI1, and anti-GABA_B receptor antibodies in serum and CSF. A chest CT examination helped ruled out sarcoidosis. The diagnosis of multiple sclerosis (MS) was less likely given the lack of typical attacks and MRI lesions. Finally, the diagnosis of CLIPPERS was established according to the clinical manifestations and typical radiologic findings. Her good response to corticosteroids further supported the diagnosis. Although the neuropathological findings in CLIPPERS have been reported distinct from multiple sclerosis (MS), neuromyelitis optica (NMO), sarcoidosis, neuro-Behçet’s disease, glioma, and lymphoma, they are by no means specific.^[6]

Table 1

Diagnostic workup.

Blood count and kidney and liver functions	Normal
Erythrocyte sedimentation rate	5 mm per hour (normal range: 0–20 mm/h)
Immunoglobulins and complement	Normal
Anti-nuclear, anti-neutrophil cytoplasmic, anti-DNA, anti-SSA/SSB antibodies and rheumatoid factor	Negative
Anti-NMDA receptors, anti-AMPA1 receptors, anti-AMPA2 receptors, anti-CASPR2, anti-LGI1 and anti-GABA _B receptors antibodies in serum and CSF	Negative
Anti-neuronal antibodies (anti-Yo, -Hu, -Ri, -amphiphysin, -CV2, -PNMA2) in serum and CSF	Negative
Serum HIV, HBV, HCV	Negative
CSF	WBC: $4 \times 10^6/L$ (normal range: $0-0.8 \times 10^6/L$); RBC: $0 \times 10^6/L$; Pro: 0.76 g/L (normal range: 0.15–0.45 g/L); Glu: 3.08 mmol/L (normal range: 2.3–4.1 mmol/L); CEA: 5.75 ng/mL (normal range: <5.00 ng/mL)
Blood tumor markers	

AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CASPR2 = contactin-associated protein 2, CEA = carcino-embryonic antigen, CSF = cerebrospinal fluid, GABA = γ -aminobutyric acid, Glu = glucose, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, LGI1 = Leucine-rich glioma inactivated 1, NMDA = N-methyl-D-aspartate, Pro = protein, RBC = red blood cell, SSA/SSB = anti-Sjögren’s-syndrome-related antigen A/B, WBC = white blood cell.

In this case, we did not perform biopsy since it is an invasive procedure and the patient has responded well to corticosteroids. Brain biopsy is necessary when alternative etiologies cannot be ruled out through vigorous investigations, when atypical clinical or neuroimaging findings are noted or when the patients are evidently resistant to GCS.^[6]

Characteristic clinical features of CLIPPERS related to involvement of the brainstem, cranial nerves and the cerebellum include gait ataxia, dysarthria, diplopia, and altered facial sensation. Cases may present with cognitive dysfunctions like mnemonic deficits and the dys-executive syndrome.^[2,7,6] Although cerebellar lesions can cause the cerebellar cognitive affective syndrome which includes impairments in executive, visual-spatial, and linguistic abilities.^[8] The cognitive dysfunctions cannot be completely explained by involvement of the cerebellum and the brainstem. Two reported cases with cognitive dysfunctions developed cerebral atrophy over time. Our patient also presented with cognitive deficits including memory loss and calculation ability decline. The cognitive impairments might be due to the lesions in the hippocampus and amygdaloid nucleus. Although MRI showed resolution of gadolinium enhancement lesions after 4-month immunosuppressive treatment without atrophy, more follow-up are necessary. According to the cases which have been reported, the onset age of CLIPPERS ranges from 13 to 86 years. The mean age at onset is 50.2 years. Both sexes are comparably affected. The common symptoms of CLIPPERS are gait ataxia, dysarthria, diplopia, and altered facial sensation in the cases. Eyeball movement disorder and cognitive dysfunctions are relatively rare.

Maintenance treatment is important to prevent further relapses. In this case, azathioprine (100 mg/d) was administered as a corticosteroid sparing agent when methylprednisolone was tapered to 20 mg per day and the patient's condition was stable. Then, we used azathioprine as a monotherapy after oral methylprednisolone was discontinued. This therapy is different from most of the reported strategies. Although corticosteroid sparing agents were proposed to be used to reduce the dose of corticosteroids in long-term therapy in view of their multiple side effects, a majority of the patients used oral corticosteroids alone to maintain remission. Suer et al^[9] reported a case who was on azathioprine as maintenance treatment without glucocorticosteroids; follow-up clinical and radiological investigations at the 3rd, 6th, and 12th months were normal. However, some immunosuppressive agents alone appeared incapable of maintaining remission.^[1,6]

Our case is unique in two aspects. Firstly, her main clinical symptom at onset was inability to move her eyeballs horizontally. Oculomotor abnormalities including gaze palsy, oculomotor palsies, internuclear ophthalmoplegia, and one-and-a-half syndrome are not rare in patients with CLIPPERS. But horizontal eyeball akinesia as an initial manifestation has not been reported. The symptom may relate to involvement of medial longitudinal fasciculus and paramedian pontine reticular formation bilaterally. Secondly, we verified the effect of azathioprine as a monotherapy in maintenance treatment in the case. Most of the cases reported before was treated with oral corticosteroids alone or with additional GCS-sparing agents to maintain remission, because many immunosuppressive agents alone were believed to be incapable of maintaining remission.^[1,6] However, chronic glucocorticosteroid therapy is limited by side effects. So, it is important to find some immunosuppressive agents as alternative therapy. More follow-up and evidences are necessary to further prove the effect of azathioprine.

We searched PubMed database until January 1, 2016, for articles published with the search terms "CLIPPERS". We also reviewed the reference lists of the papers identified by this search. Forty one case studies and a review were included, comprising 60 patients with CLIPPERS. The possible etiology and pathogenesis, clinical characteristics, neuroimaging, diagnostic criteria, and therapeutic management of this disorder are summarized.

The pathogenesis of CLIPPERS remains unknown; no obvious causes are identifiable in most of the patients. Hillesheim et al^[10] reported a case of CLIPPERS following influenza vaccination. Ortega et al^[11] described a patient with MS who developed CLIPPERS shortly after natalizumab withdrawal. Mashima et al^[12] reported a case who developed CLIPPERS after treatment for Hodgkin's lymphoma. Wang et al^[13] reported a case of CLIPPERS following herpes zoster infection. To explain the particular features of CLIPPERS, Pittock et al^[1] proposed an organ-specific autoimmunity as its possible basis; the target autoantigen of the specific immune-mediated process is likely localized in the perivascular regions. Considering the anatomic arrangement of small intra-axial veins of the central nervous system (CNS), the predominant involvement of brainstem structures might be related to a primary CNS venous inflammatory disorder.^[14] Elevated levels of immunoglobulin IgE in serum were noted in several CLIPPERS cases,^[2,15] suggesting that immediate and late allergic reactions may contribute to the pathogenesis of CLIPPERS. Interestingly, anti-tuberculous therapy was effective for CLIPPERS.^[16] Since rifampicin can inhibit Th17 differentiation and functions, this suggests that CLIPPERS may be a Th17-mediated autoimmune disease.

The cardinal clinical features of CLIPPERS are subacute onset of cerebellar and brainstem syndromes.^[1] The onset age of CLIPPERS varies (mean age: 50.2, range: 13–86 years). More men are affected by the disorder than women (Table 2) though the difference is not significant. Symptoms at onset are usually gait ataxia and diplopia.^[1,7] Dysarthria, nystagmus, eye movement abnormalities, dizziness, altered facial sensation, pseudobulbar palsy, cognitive deficits, tremor, and other symptoms may appear simultaneously or successively in the course of CLIPPERS.^[1,7,23] Tetraparesis and altered sensation of extremities may appear when spinal cord is involved. Tetraparesis may also happen due to lesions in the brainstem which involve the corticospinal tract. According to 60 previously reported cases, most common symptoms of CLIPPERS is ataxia, which was observed in 58 out of 60 cases. Dysarthria (n=38), diplopia (n=36), paraparesis/tetraparesis/hemiparesis/paresis of a single extremity (n=21), nystagmus (n=20), altered sensation or tingling of the face (n=16), altered sensation/sensory loss of extremities (n=16), oculomotor abnormalities (n=15) are also common characteristics of CLIPPERS (Table 3). Systemic symptoms are generally not a feature of CLIPPERS.^[1] The clinical course without specific treatment seems to be relapsing-remitting in nature.^[14] MRI may show no abnormalities at the onset of the disease.^[30] Serial MRI examinations may be necessary when CLIPPERS is suspected. The hallmark feature of CLIPPERS on MRI is punctate and curvilinear gadolinium enhancement in a "pepper-like appearance" with a perivascular pattern centered on the pons.^[1] The gadolinium enhancement may decrease after immunosuppressive therapy. The lesions are typically less numerous and smaller as distance from the pons increases,^[1] which may extend into adjacent CNS structures including spinal cord, medulla oblongata, midbrain, cerebellar, corpus callosum, and thalamus. Supratentorial regions may also

Table 2
Reported cases of CLIPPERS.

Author/Source	Cases	Gender		Age at onset (years)
		Male	Female	
Pittock et al ^[1]	8	3	5	Range 16–86 (mean 52.4)
Sempere et al ^[17]	1	1	0	68
Saigal et al ^[18]	2	1	1	53, 56
Wijntjes et al ^[19]	1	1	0	63
Wang et al ^[13]	1	0	1	62
Bag et al ^[20]	1	1	0	23
Kerrn-Jespersen et al ^[21]	3	2	1	42, 58
Smith et al ^[22]	1	0	1	55
Ha et al ^[23]	2	0	2	56, 65
Suer et al ^[9]	1	1	0	51
Gul et al ^[24]	1	0	1	70
Weng et al ^[25]	1	1	0	34
Reddy et al ^[26]	1	0	1	50
Marinho et al ^[27]	1	1	0	35
Esmailzadeh et al ^[28]	1	1	0	68
Moreira et al ^[29]	1	0	1	76
Taieb et al ^[30]	1	1	0	13
List et al ^[31]	1	0	1	69
Kastrup et al ^[2]	3	3	0	56, 57, 58
Hillesheim et al ^[10]	1	1	0	80
Ortega et al ^[11]	1	0	1	Unknown
Tohge et al ^[15]	1	0	1	54
Buttmann et al ^[32]	1	0	1	45
Mélé et al ^[16]	1	1	0	64
Mashima et al ^[12]	1	1	0	31
Simon et al ^[7]	5	4	1	Range 20–65 (mean 43.4)
Pesaresi et al ^[33]	1	1	0	40
Tan et al ^[34]	1	1	0	53
Gabilondo et al ^[3]	1	0	1	28
Duprez et al ^[35]	1	0	1	70
Taieb et al ^{[8],*}	11	8	3	Range 13–64 (mean 45.5)
Kleinschmidt-DeMasters et al ^[36]	1	0	1	49
Lefaucheur et al ^[37]	1	1	0	48
Total	60	35	25	–

CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids.

* One case reported in this article which was finally diagnosed as central nervous system (CNS) B-cell lymphoma^[5] was excluded.

be involved, such as thalami, capsula interna, basal ganglia, and cerebral white matter, etc.^[7,24] Lesions may present as mild to moderate hyperintensity on T2 and FLAIR images. Of note is that mass effect does not exclude the diagnosis of CLIPPERS as mass effect might be observed in some patients during relapses.^[14] Atrophy of the cerebellum and brachium pontis may appear in the long course of the disease or in severe cases,^[7,35] suggestive of neurodegenerative features of the disease.^[21]

There have been no validated diagnostic criteria of CLIPPERS until now. Diagnosis of CLIPPERS is based on clinical, radiological, laboratory and CSF investigations, and brain biopsy when necessary. Other disorders that present with similar lesions should be carefully excluded with extensive investigations. Simon et al^[7] highlighted the core clinical, radiological, and histopathological features of the syndrome (Table 4). A diagnostic criteria summarized by Taieb et al^[38] include brainstem signs and symptoms, cerebral punctate and curvilinear gadolinium enhancements centered on the pons and cerebellum, good clinical and radiological responsiveness to GCS, absence of evidence of an alternative diagnosis, a relapsing-remitting course fulfilling the criteria above, and perivascular lymphohistocytic

Table 3
Reported clinical characteristics of CLIPPERS.

Clinical characteristics	Number of patients
Ataxia (gait ataxia, stance ataxia, truncal ataxia, limb ataxia)	58
Dysarthria	38
Diplopia	36
Paraparesis, tetraparesis, hemiparesis, paresis of a single extremity	21
Nystagmus (horizontal, vertical, gaze evoked nystagmus)	20
Altered sensation or tingling of the face (facial tingling, par-/dysaesthesias, hypaesthesia),	16
Altered sensation/sensory loss of extremities	16
Oculomotor abnormalities (gaze palsy, oculomotor palsies, internuclear ophthalmoplegia, one-and-a-half syndrome)	15
Facial nerve palsy	13
Dizziness	11
Fatigue	11
Dysphagia	9
Pseudobulbar affect (pathological/involuntary crying or laughter, labile affect)	8
Vertigo	8
Nausea	6
Psychomotor slowing	6
Hyperacusis, hearing impairment, tinnitus	6
Headaches	4
Tremor (action, Holmes tremor)	4
Cognitive deficits	3
Decreased vibration sense	3
Dysgeusia	2
Hiccup	2
Tongue weakness	1

Based on 60 previously reported cases.^[1–3,10–16,7,23,24,30,35,21,31,32,34,25,36,18,17,19,20,22,9,26–29,33,37]

CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids.

infiltrates on brainstem biopsy. Differential diagnoses of CLIPPERS include CNS lymphoma, lymphomatoid granulomatosis, CNS infections, neurosarcoidosis, neuro-Behçet’s disease, Sjögren’s syndrome, MS, NMO, primary angiitis of the CNS, CNS histiocytosis, acute disseminated encephalomyelitis, Bickerstaff brainstem encephalitis, other inflammatory demyelinating CNS diseases, other autoimmune encephalitides, brainstem tumors, and paraneoplastic disorders.^[1,2,10,11,7,31,39,40,41,32,42,43,6]

The unanimous therapy plan is absent due to the relative few cases reported thus far. It is believed that high-dose intravenous methylprednisolone (1 g daily for 5 days) are necessary as soon as possible after a diagnosis has been established so as to prevent progressive clinical worsening.^[14,7] Patients usually show early and marked clinical improvement within several days after the use of GCS. Long-term oral corticosteroids (>20 mg/day) seem sufficient to maintain remission and prevent further relapses.^[1,3,14] To avoid the side effects of steroids, immunosuppressive agents have been proposed as an add-on choice.^[1,3,14] Azathioprine without GCS may be effective to maintain remission.^[9] High-dose intravenous methylprednisolone followed by oral GCS should also be started as early as possible in case of relapses. Gabilondo et al^[3] tried to taper GCS to 5 mg/day and to use intravenous immunoglobulins (0.4 g/kg/day for 5 days) on a patient, while failed to prevent relapses; cerebellar symptoms reappeared in 2 days after the last dose of intravenous immunoglobulins. It is debatable whether oral hydroxychloroquine is effective. Pittock et al^[1] attempted to use oral hydroxychloroquine instead of prednisone to maintain the remission of the symptoms, whereas brain MRI showed

Table 4**Core features of CLIPPERS.****Clinical**

Subacute progressive ataxia and dysarthria

A range of other clinical features referable to brainstem pathology plus cognitive and spinal features occur in some patients

Radiological

- (a) Numerous punctate or nodular enhancing lesions bilaterally in at least two of the three following anatomical locations: pons, brachium pontis, cerebellum
- (b) Individual radiological lesions are small but may coalesce to form larger lesions (mass effect has not been seen and to date suggests an alternative diagnosis)
- (c) Lesions may occur in the spinal cord, basal ganglia or cerebral white matter but should be of decreasing density with increasing distance from the hindbrain
- (d) Absence of the following radiological features
 - (i) Restricted diffusion on diffusion weighted imaging
 - (ii) Marked hyperintensity on T2 weighted images
 - (iii) Abnormal cerebral angiography

Corticosteroid responsiveness

Prompt and significant clinical and radiological response to corticosteroids

Histopathological

- (a) White matter perivascular lymphohistiocytic infiltrate with or without parenchymal extension
- (b) Infiltrate contains predominantly CD3+ and CD4+ lymphocytes
- (c) Absence of the following histopathological characteristics:
 - (i) Monoclonal or atypical lymphocyte population
 - (ii) Necrotizing granulomas or giant cells
 - (iii) Histological features of vasculitis (destruction of the vessel wall, fibrinoid necrosis, leukocytoclasia, fibrin thrombi)

Differential diagnoses, including neurosarcoidosis, Sjögren syndrome, neuro-Behçet disease, vasculitis, and lymphoma should be excluded

Adapted from Simon et al.^[7]

CLIPPERS=chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids.

radiological progression of the inflammatory lesions. However, Tan et al^[34] reported a case who was successfully treated with hydroxychloroquine to induce and maintain remission for 4 years. Mélé et al^[16] reported a case with CLIPPERS who was initially misdiagnosed with CNS tuberculosis. The patient was treated with antituberculous therapy including rifampicin, isoniazid, and pyrazinamide and showed clinical and radiologic improvement after the treatment. Combination of levodopa and botulinum toxin injections may be effective for patients of CLIPPERS with tremor.^[23] Antiviral therapy is needed when CLIPPERS is accompanied by chronic HBV infection.^[25]

Taieb et al^[14] observed 42 relapses among 12 patients in a mean follow-up period of 5.5 years. On average, 0.63 annual relapses per patient. Recurrence of disease can be provoked by attempts to withdraw or taper GCS below a particularly lower dose limit.^[1–3] Long-term GCS treatment seemed necessary for most of the patients with CLIPPERS. Progressive clinical worsening was seen during relapses, which may leave residual neurological sequelae.^[6] Inflammatory vessel occlusion was described in biopsy specimens of CLIPPERS^[32,36] and stroke mimicking relapses was reported.^[44] Saigal and Quencer^[18] reported a case of CLIPPERS who had multiple acute lacunar infarcts in basal ganglia. These cases suggest a possible relationship between stroke and CLIPPERS. More follow-up studies are necessary to better delineate the prognosis of CLIPPERS.

In summary, CLIPPERS is an immune-mediated inflammatory disorder of the brainstem, which has been increasingly reported. Irreversible neuronal damage may occur in CLIPPERS.^[35] Thus, early usage of high-dose intravenous methylprednisolone is necessary when MRI shows punctate and curvilinear gadolinium

enhancement in a “pepper-like appearance” and differential diagnoses are excluded.

4. Informed consent

The reporting of the above case was approved by the ethics committee of the First Hospital of Jilin University, Changchun, China. Though written informed consent was not obtained, the patient’s information was anonymized and de-identified.

References

- [1] Pittock SJ, Debruyne J, Krecke KN, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *Brain* 2010;133:2626–34.
- [2] Kastrup O, van de Nes J, Gasser T, et al. Three cases of CLIPPERS: a serial clinical, laboratory and MRI follow-up study. *J Neurol* 2011; 258:2140–6.
- [3] Gabilondo I, Saiz A, Graus F, et al. Response to immunotherapy in CLIPPERS syndrome. *J Neurol* 2011;258:2090–2.
- [4] Odaka M, Yuki N, Yamada M, et al. Bickerstaff’s brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. *Brain* 2003;126(Pt 10):2279–90.
- [5] Taieb G, Uro-Coste E, Clanet M, et al. A central nervous system B-cell lymphoma arising two years after initial diagnosis of CLIPPERS. *J Neurol Sci* 2014;344:224–6.
- [6] Dudesek A, Rimmele F, Tesar S, et al. CLIPPERS: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. Review of an increasingly recognized entity within the spectrum of inflammatory central nervous system disorders. *Clin Exp Immunol* 2014;175:385–96.
- [7] Simon NG, Parratt JD, Barnett MH, et al. Expanding the clinical, radiological and neuropathological phenotype of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *J Neurol Neurosurg Psychiatry* 2012;83:15–22.
- [8] Gordon N. The cerebellum and cognition. *Eur J Paediatr Neuro* 2007;11:232–4.
- [9] Suer D, Yusifova L, Arsava EM, et al. A case report of CLIPPERS (chronic lymphocytic inflammation with pontocerebellar perivascular enhancement responsive to steroids) syndrome. *Clin Neuroradiol* 2015;25:61–3.
- [10] Hillesheim PB, Parker JR, Parker JCJ, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids following influenza vaccination. *Arch Pathol Lab Med* 2012; 136:681–5.
- [11] Ortega MR, Usmani N, Parra-Herran C, et al. CLIPPERS complicating multiple sclerosis causing concerns of CNS lymphoma. *Neurology* 2012;79:715–6.
- [12] Mashima K, Suzuki S, Mori T, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) after treatment for Hodgkin’s lymphoma. *Int J Hematol* 2015; 102:709–12.
- [13] Wang L, Holthaus EA, Jimenez XF, et al. MRI evolution of CLIPPERS syndrome following herpes zoster infection. *J Neurol Sci* 2015;348: 277–8.
- [14] Taieb G, Duflos C, Renard D, et al. Long-term outcomes of CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) in a consecutive series of 12 patients. *Arch Neurol* 2012;69:847–55.
- [15] Tohge R, Nagao M, Yagishita A, et al. A case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) in East Asia. *Intern Med* 2012;51:1115–9.
- [16] Mélé N, Guiraud V, Labauge P, et al. Effective antituberculous therapy in a patient with CLIPPERS: new insights into CLIPPERS pathogenesis. *Neurol Neuroimmunol Neuroinflamm* 2014;1:e6.
- [17] Sempere AP, Mola S, Martin-Medina P, et al. Response to immunotherapy in CLIPPERS: clinical, MRI, and MRS follow-up. *J Neuroimaging* 2013;23:254–5.
- [18] Saigal G, Quencer R. Acute lacunar infarcts in CLIPPERS: is the chronic infiltrative lymphocytic perivascular disease process to blame? *Neuro-radiol J* 2013;26:629–35.
- [19] Wijntjes J, Wouda EJ, Siegert CE, et al. Need for prolonged immunosuppressive therapy in CLIPPERS—a case report. *BMC Neurol* 2013;13:49.

- [20] Bag AK, Davenport JJ, Hackney JR, et al. Case 212: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. *Radiology* 2014;272:940–7.
- [21] Kerrn-Jespersen BM, Lindelof M, Illes Z, et al. CLIPPERS among patients diagnosed with non-specific CNS neuroinflammatory diseases. *J Neurol Sci* 2014;343:224–7.
- [22] Smith A, Matthews Y, Kossard S, et al. Neurotropic T-cell lymphocytosis: a cutaneous expression of CLIPPERS. *J Cutan Pathol* 2014;41:657–62.
- [23] Ha AD, Parratt JD, Babu S, et al. Movement disorders associated with CLIPPERS. *Mov Disord* 2014;29:148–50.
- [24] Gul M, Chaudhry AA, Chaudhry AA, et al. Atypical presentation of CLIPPERS syndrome: a new entity in the differential diagnosis of central nervous system rheumatologic diseases. *J Clin Rheumatol* 2015;21:144–8.
- [25] Weng CF, Chan DC, Chen YF, et al. Chronic hepatitis B infection presenting with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS): a case report. *J Med Case Rep* 2015;9:266.
- [26] Reddy SM, Lath R, Swain M, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS): a case report and review of literature. *Ann Indian Acad Neurol* 2015;18:345–7.
- [27] Marinho PB, Montanaro VV, Barroso Freitas MC, et al. CLIPPERS syndrome: case report in a Brazilian patient with a long term disease evolution. *Mult Scler Relat Disord* 2015;4:311–4.
- [28] Esmailzadeh M, Yildiz O, Lang JM, et al. CLIPPERS syndrome: an entity to be faced in neurosurgery. *World Neurosurg* 2015;84:2077e1–3.
- [29] Moreira I, Cruto C, Correia C, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS): postmortem findings. *J Neuropathol Exp Neurol* 2015;74:186–90.
- [30] Taieb G, Wacongne A, Renard D, et al. A new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids with initial normal magnetic resonance imaging. *Brain* 2011;134(Pt 8):e182author reply e3.
- [31] List J, Lesemann A, Wiener E, et al. A new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. *Brain* 2011;134(Pt 8):e185author reply e6.
- [32] Buttman M, Metz I, Brecht I, et al. Atypical chronic lymphocytic inflammation with pontocerebellar perivascular enhancement responsive to steroids (CLIPPERS), primary angitis of the CNS mimicking CLIPPERS or overlap syndrome? A case report. *J Neurol Sci* 2013;324:183–6.
- [33] Pesaresi I, Sabato M, Desideri I, et al. 3.0T MR investigation of CLIPPERS: role of susceptibility weighted and perfusion weighted imaging. *Magn Reson Imaging* 2013;31:1640–2.
- [34] Tan BL, Agzarian M, Schultz DW. CLIPPERS: induction and maintenance of remission using hydroxychloroquine. *Neurol Neuroimmunol Neuroinflamm* 2015;2:e56.
- [35] Duprez TP, Sindic CJ. Contrast-enhanced magnetic resonance imaging and perfusion-weighted imaging for monitoring features in severe CLIPPERS. *Brain* 2011;134(Pt 8):e184author reply e6.
- [36] Kleinschmidt-DeMasters BK, West M. CLIPPERS with chronic small vessel damage: more overlap with small vessel vasculitis? *J Neuropathol Exp Neurol* 2014;73:262–7.
- [37] Lefaucheur R, Bouwyn JP, Ahtoy P, et al. Teaching neuroImages: punctate and curvilinear enhancement peppering the pons responsive to steroids. *Neurology* 2011;77:e57–8.
- [38] Taieb G, Duran-Pena A, de Chamfleury NM, et al. Punctate and curvilinear gadolinium enhancing lesions in the brain: a practical approach. *Neuroradiology* 2015;58:221–35.
- [39] Jones JL, Dean AF, Antoun N, et al. 'Radiologically compatible CLIPPERS' may conceal a number of pathologies. *Brain* 2011;134(Pt 8):e187.
- [40] Limousin N, Praline J, Motica O, et al. Brain biopsy is required in steroid-resistant patients with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *J Neurooncol* 2012;107:223–4.
- [41] De Graaff HJ, Wattjes MP, Rozemuller-Kwakkel AJ, et al. Fatal B-cell lymphoma following chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. *JAMA Neurol* 2013;70:915–8.
- [42] Ferreira RM, Machado G, Souza AS, et al. CLIPPERS-like MRI findings in a patient with multiple sclerosis. *J Neurol Sci* 2013;327:61–2.
- [43] Keegan BM, Pittock SJ. Cutting-edge questions about CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids). *Arch Neurol* 2012;69:819–20.
- [44] Lefaucheur R, Bourre B, Ozkul-Wermester O, et al. Stroke mimicking relapse in a patient with CLIPPERS syndrome. *Acta Neurol Belg* 2015;115:735–6.