Curr Neurol Neurosci Rep (2017) 17: 65
DOI 10.1007/s11910-017-0773-7

CLIPPERS

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Published online: 19 July 2017

Abstract
Purpose of Review Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently described treatable, inflammatory, brainstem predominant encephalomyelitis. The diagnosis of CLIPPERS is challenging without a specific biomarker, and thus it is important to consider if both the clinical and radiographic features are consistent with the diagnosis, or rather a disease mimicker.
Recent Findings Many patients with CLIPPERS-like lesions have been described in the literature with follow-up revealing a range of alternative diagnoses, such as malignancies, vasculitis, and other specific inflammatory diseases. As a result, some have proposed that CLIPPERS might represent a premalignancy state or simply an initial clinical syndrome of a variety of possible etiologies.
Summary We describe the typical clinical, radiographic, and pathological features of CLIPPERS and emphasize consideration for alternative diagnoses when findings are not classic. A recommended diagnostic evaluation and initial treatment plan is provided.

Keywords CLIPPERS · Brainstem encephalitis · Encephalomyelitis · Vasculitis · Lymphoma · PCNSL

This article is part of the Topical Collection on *Demyelinating Disorders*

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Introduction

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a brainstem predominant encephalomyelitis with punctate curvilinear post-gadolinium contrast enhancement centered in the pons and cerebellum on brain MRI, with biopsy findings consisting of prominent perivascular CD3+ T cell predominant lymphocytic inflammation, and an exquisite clinical and radiographic response to corticosteroids [1]. Since the original description of the syndrome, several other groups have reported similar cases [2, 3], supporting the existence of the syndrome. The absence of a definitive diagnostic biomarker has led to some confusion in the field, with primary central nervous system (CNS) malignancy [4, 5•, 6–8], systemic T cell lymphoma [9], Hodgkin's lymphoma [10], chronic hepatitis B infection [11], myelin oligodendrocyte glycoprotein (MOG) antibodies [12], CNS lymphomatoid granulomatosis [13], and multiple sclerosis (MS) [14, 15] all being described in association with neuroimaging features similar to CLIPPERS. The purpose of this review is to summarize the clinical, radiological, and pathological features of CLIPPERS and to describe a suggested evaluation and treatment plan when faced with a patient with suspected CLIPPERS.

Clinical Findings

CLIPPERS is a brainstem predominant encephalomyelitis, with clinical and radiographic features predominating in the pons and cerebellum. Given this predilection, it is not surprising that the most common clinical features include gait ataxia, diplopia, dysarthria, and altered facial sensation accompanied by additional brainstem, myelopathy, and cognitive findings [2, 3, 16••]. Additional features include pseudobulbar affect

[2, 17], tinnitus [2], tremor [16••, 17], nystagmus [2, 3, 16••], long-tract signs [16••, 17–19], paraparesis [1, 3, 16••], dizziness, nausea, and dysgeusia. Symptoms typically evolve over weeks or months. A rapid onset of symptoms progressing to severe deficits within days is atypical for CLIPPERS. The usual age of onset is in midlife, but a wide range has been reported (median 45.5 years; range 16–86 years) [1]. There is no clear gender predilection. None of the clinical characteristics commonly seen in CLIPPERS are pathognomonic; however, a predominance of clinical features that are not commonly seen in CLIPPERS at presentation or relapse, such as optic neuritis, seizures or systemic symptoms, should prompt a reevaluation of the diagnosis.

Laboratory Findings

There are no specific serum laboratory markers available to make the diagnosis of CLIPPERS. Patients with CLIPPERS have not been found to have aquaporin-4 (AQP4)-IgG, Glial fibrillary acidic protein (GFAP)-IgG, or other neural-specific autoantibodies. Laboratory testing is useful to exclude alternative diagnoses, such as HIV, vasculitis, and autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy [20].

There is also no specific cerebrospinal fluid abnormality in CLIPPERS. The most common finding is a mild elevation in protein [1, 3]. Oligoclonal bands and IgG index are elevated in some cases. A highly inflammatory cerebrospinal fluid with a marked pleocytosis (>150 total nucleated cells/mcL), marked elevation in protein, and/or hypoglycorhacia should prompt consideration of an alternative diagnosis.

Neuroimaging

Brain MRI in CLIPPERS is characterized by punctate, curvilinear post-gadolinium enhancement centered in the pons and cerebellum [1, 3, 16••, 21, 22]. Most lesions are less than 3 mm in diameter, and larger asymmetric lesions should prompt evaluation for alternate diagnoses. Lesions become less numerous further away from the pons, but can extend into the cerebral hemispheres and spinal cord. The area of T2-hyperintensity tends to be similar to the area of post-gadolinium enhancement, as shown in Fig. 1. Despite significant clinical disability, T2 and T2-FLAIR images may be relatively unrevealing, with lesions readily apparent on post-gadolinium T1-weighted images [3]. Published cases of CLIPPERS-like MRI features which have ultimately had an alternate diagnosis have included patients with pial enhancement and both clinical and radiological worsening on corticosteroid treatment [23]; asymmetric contrast-enhancing lesions with a larger area of T2 hyperintensity than post-gadolinium enhancement [5•, 6]; and larger, asymmetric areas of contrast enhancement than previously described [4], underscoring the necessity of only considering "typical" MRI features as being compatible with CLIPPERS.

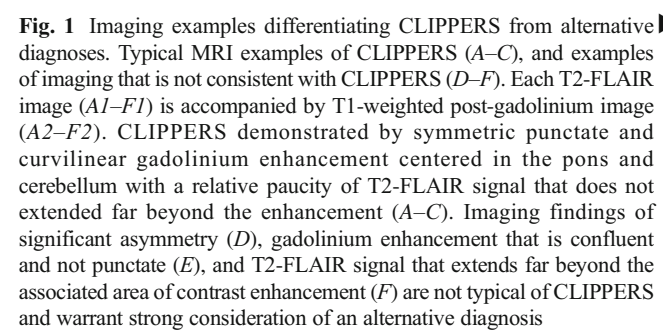


Fig. 1 Imaging examples differentiating CLIPPERS from alternative diagnoses. Typical MRI examples of CLIPPERS (*A–C*), and examples of imaging that is not consistent with CLIPPERS (*D–F*). Each T2-FLAIR image (*A1–F1*) is accompanied by T1-weighted post-gadolinium image (*A2–F2*). CLIPPERS demonstrated by symmetric punctate and curvilinear gadolinium enhancement centered in the pons and cerebellum with a relative paucity of T2-FLAIR signal that does not extended far beyond the enhancement (*A–C*). Imaging findings of significant asymmetry (*D*), gadolinium enhancement that is confluent and not punctate (*E*), and T2-FLAIR signal that extends far beyond the associated area of contrast enhancement (*F*) are not typical of CLIPPERS and warrant strong consideration of an alternative diagnosis

Lesion distribution outside of the pons and adjacent brainstem with extension through the basal ganglia and spinal cord (cervical and thoracic) can be seen [1], and the lesion burden tends to be lower further away from the pons and cerebellum. More extensive areas of involvement have been described, including bilateral posterior limbs of the internal capsule [19], thalamus [3], diffuse gadolinium peppering throughout the white matter of the entire brain (including the corticosubocortical region) [24, 25], and extensive cervical [18] and thoracic spinal cord involvement [19, 26].

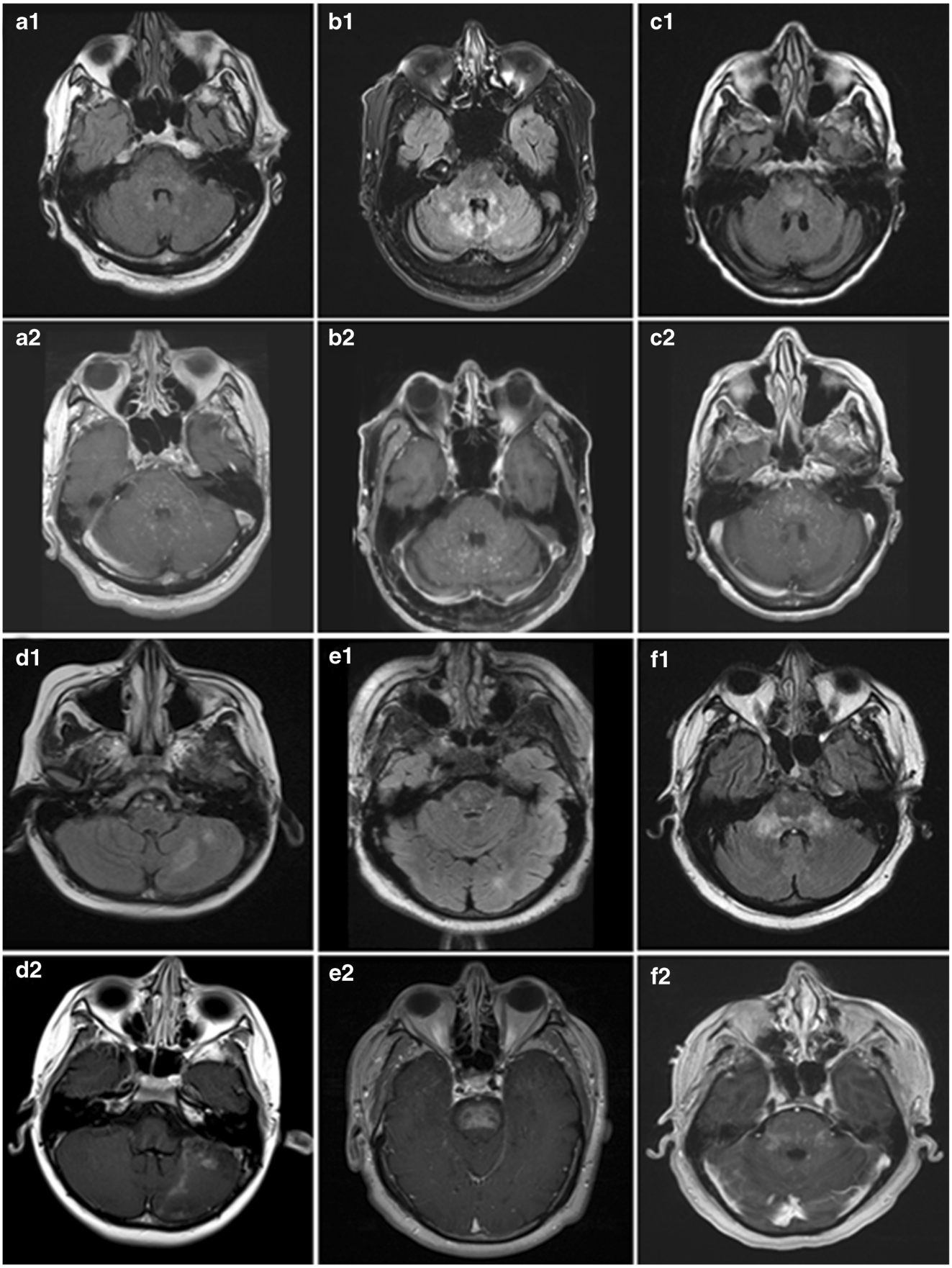
Responsiveness to corticosteroids constitutes a key element of the diagnosis of CLIPPERS. In the majority of cases, the enhancing lesions tend to resolve completely within weeks following treatment with corticosteroids, although lesions may recur if corticosteroids are withdrawn. If rapid resolution of enhancement is not seen after corticosteroids, the working diagnosis of CLIPPERS should be reconsidered [4]. Worsening of enhancement during corticosteroid treatment, a lack of robust radiological response, a change in the predominant imaging pattern, or a significantly different area of involvement on follow-up imaging should prompt consideration of alternative etiologies [6].

Cerebellar atrophy and generalized cerebral atrophy have been observed, despite resolution of contrast-enhancing lesions with treatment, and more pronounced atrophy has been associated with persistent cognitive impairment [17]. Brainstem and spinal cord atrophy have also been seen in CLIPPERS [2].

The role of advanced imaging techniques in the diagnosis of CLIPPERS is uncertain. MR spectroscopy (MRS) [6] and cerebral angiography [3] may be helpful in identifying patients with alternate diagnoses such as lymphoma or vasculitis.

Neuropathology

No pathological hallmark has been identified for the diagnosis of CLIPPERS. As such, the primary reason to perform a brain biopsy is to exclude findings concerning for an alternative diagnosis. Specifically, findings consistent with vasculitis, granulomatous disease, infection, malignancy, or other


a1
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neuroimflammatory disease should not be seen. The eloquent nature of areas typically involved in CLIPPERS has led to reticence to recommend biopsy in all patients with CLIPPERS [27]. However, in carefully selected patients at centers that perform a high volume of posterior fossa biopsies, the operative risk is similar to hemispheric biopsies [28•].

Pathological findings in CLIPPERS are defined by perivascular inflammation with CD3 reactive T lymphocytes (predominantly CD4 positive), activated microglia, CD68 positive histiocytes, and a lesser degree of accompanying CD20 positive B lymphocytes [1]. The lack of granulomas and lymphocyte clonality on biopsy in patients with CLIPPERS is felt to reasonably exclude lymphomatoid granulomatosis (LYG) at the initial diagnosis [3]. However, perivascular T cell infiltrates can also be seen in primary CNS lymphoma sentinel lesions and grade I LYG, indicating that the typical pathological findings in CLIPPERS as reported to date are non-specific and require complete clinical assessment and follow-up to secure the diagnosis of CLIPPERS [29]. An important consideration is that corticosteroid treatment before biopsy and sampling error may alter the diagnostic accuracy and lead to non-specific inflammatory findings on brain pathology for some diseases, such as CNS lymphoma [30, 31].

Response to Treatment

A robust clinical and radiological response to corticosteroid treatment is a classic feature of CLIPPERS. This finding is not specific though, as other inflammatory and neoplastic disorders often respond to corticosteroids. Recrudescence of symptoms with post-gadolinium enhancement on brain MRI is the norm in the absence of prolonged treatment and with low doses of corticosteroids (≤ 20 mg prednisone daily) [2]. Symptoms of relapse related to CLIPPERS are similar to those of the initial presentation. Depending on the degree of deficits and duration of untreated disease, not all patients have complete clinical recovery. Most patients should have absence of gadolinium-enhancing lesions on brain MRI within weeks of commencing corticosteroids.

Red Flags for Alternate Conditions

Perhaps more important than recognizing the typical features of CLIPPERS, a clinician should be aware of findings that raise concern for an alternative diagnosis. Some of the most commonly encountered clinical red flags when considering CLIPPERS include lack of significant response to corticosteroids, lack of typical brainstem predominant findings, progression to severe deficits within days, fever or marked B symptoms, early-onset of seizures, depressed level of consciousness, and any other findings localizing outside the CNS. Although atypical cases of CLIPPERS have been reported with suspected peripheral nerve [19], cutaneous [32•], pulmonary [9], salivary gland [17], and ocular involvement [17], diagnosis of atypical CLIPPERS may lead to overdiagnosis in the absence of a specific diagnostic biomarker. Brain MRI lesions with significant edema or mass effect, normal neuroimaging while symptomatic, and ring-enhancing brain lesions are all inconsistent with CLIPPERS [2]. Although in some cases an asymmetric lesion distribution can occur, significant asymmetry is suggestive of an alternate process [5•]. Cortical, leptomeningeal, dural, and hypothalamic-pituitary lesion locations on MRI are not currently recognized as features of CLIPPERS [33••].

Pathogenesis

The underlying pathogenesis of CLIPPERS is unclear. A neoplastic or paraneoplastic etiology has been proposed, following association of some reported cases of CLIPPERS with malignancy [9, 22, 34]. The majority of cases do not have a malignancy, however, either at presentation or follow-up. A neural autoantibody marker has not been found in CLIPPERS. Vasculitis has similarly been proposed as the etiology; however, this is not supported by pathological evidence in the majority of cases. A temporal relation to vaccination [35] and herpes zoster reactivation [36] in two separate cases is supportive of an inflammatory etiology. The predominance of CD4 positive T cells and the response to immunotherapy is also supportive of an inflammatory cause [37]. In the absence of a definitive biomarker, CLIPPERS as currently understood may represent more of a syndrome rather than a unique disease [38].

Diagnostic Evaluation

A suggested initial evaluation of patients with suspected CLIPPERS is outlined in Table 1. The differential diagnosis depends on the clinical and imaging findings for a given case. Specific diagnoses to be considered include vasculitis, CNS lymphoma, intravascular lymphoma, lymphomatoid granulomatosis, neurosarcoidosis, CNS demyelinating disease, hemophagocytic lymphohistiocytosis, Behçet's disease, chronic perivascular infections (tuberculosis, neurosyphilis, Whipple's disease), autoimmune GFAP astrocytopathy [20], Erdheim-Chester disease, and Langerhans cell histiocytosis [33••]. With no definitive biomarker for CLIPPERS, consideration should be given to brain biopsy prior to initial treatment. This serves primarily to exclude CNS malignancies and vasculitis which may require a different treatment approach.

Table 1 Suggested diagnostic evaluation of suspected CLIPPERS

Blood tests	CSF	Imaging
CBC	Cell count w/ differential	MRI brain with contrast
ESR	Protein	MRI spine with contrast
CRP	Glucose	Intracranial vascular imaging
ANA	Oligoclonal bands	Body PET-CT
ENA	IgG index	
ANCA	Cytology	
ACE	Flow cytometry	
Anti-dsDNA	Whipple PCR	
RF	Paraneoplastic antibody screen	
Hepatitis B and C serology	GFAP-IgG	
Cryoglobulins	VDRL	
HIV		
Antiphospholipid antibodies		
Lyme serology		
Paraneoplastic antibody screen		
Serum LDH		
Monoclonal protein study		
GFAP-IgG		
MOG-IgG		
Tuberculosis testing		
Syphilis serology		
Serum IgE		

Abbreviations: *CBC* complete blood count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibody, *ENA* extractable nuclear antigen, *ANCA*, anti-neutrophil cytoplasmic antibodies, *Anti-dsDNA* anti-double stranded DNA, *RF* rheumatoid factor, *HIV* human immunodeficiency virus, *LDH* lactate dehydrogenase, *GFAP* glial fibrillary acidic protein, *AQP4* aquaporin 4, *MOG* myelin oligodendrocyte glycoprotein, *VDRL* venereal disease research laboratory, *MRI* magnetic resonance imaging, *PET-CT* positron emission tomography-computed tomography, *CSF* cerebrospinal fluid

Suggested Treatment Strategy

Once the diagnosis of CLIPPERS is confirmed, treatment is recommended with high-dose corticosteroids. Typical initial treatment is IV methylprednisolone 1 g daily for 5 days. Treatment thereafter should be continued with 1 mg/kg of oral prednisone daily with appropriate precautions regarding infection prevention including PCP prophylaxis, osteoporosis prevention, and weight management. Once the expected clinical and radiological improvement with corticosteroids has been achieved, the authors typically treat with a steroid-sparing agent, such as methotrexate (target dose of 22.5 mg weekly), azathioprine (2.5 mg/kg per day), or mycophenolate mofetil (2 g per day in divided doses). Patients should remain on oral prednisone at doses ≥20 mg per day until the steroid-sparing therapy is therapeutic. Intravenous immunoglobulin does not appear effective for CLIPPERS [24]. The total duration of appropriate immunotherapy in CLIPPERS is unclear, but patients should remain on therapy at least until the disappearance of enhancing lesions. The authors typically treat for a minimum of 12 months prior to withdrawing immunotherapy. Careful monitoring with brain MRI should be performed following treatment cessation.

Future Directions

The CLIPPERS syndrome is well characterized. A consensus on diagnostic criteria is necessary to facilitate research on the etiology and treatment of the condition. Identification of a reliable biomarker is crucial to better understand the spectrum of CLIPPERS, increase diagnostic specificity, and ultimately lead to improved treatment and clinical outcomes.

Conclusion

CLIPPERS is a recently described inflammatory disorder of the CNS with characteristic clinical, radiological, and pathological findings. Diagnosis requires exclusion of other mimicking diseases, and brain biopsy should be considered. Clinical

and radiographic responsiveness to corticosteroids is necessary for the diagnosis, although clinical response may be incomplete. Patients typically require prolonged immunotherapy for best outcomes.

Compliance with Ethical Standards

Conflict of Interest Nicholas L. Zalewski and W. Oliver Tobin declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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