

CLIPPERS Responsive to Cladribine as a Durable Steroid-Sparing Agent

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Abstract

Objective

We report a case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) who achieved durable and steroid-free remission after IV cladribine.

Methods

A 25 year-old man presented with progressively worsening headaches, polydipsia, dysarthria, diplopia and vertigo, and obtundation requiring respiratory support. CSF revealed lymphocytosis, and MRI revealed a perivascular pattern of punctate enhancement involving the pons. An extensive workup for inflammatory, autoimmune, infective, and malignant explanations was unrevealing. He responded dramatically to steroids, compatible with CLIPPERS as a diagnosis of exclusion. Attempts to wean prednisone over the ensuing year resulted in 2 clinical relapses and persistent punctate enhancement. Given significant steroid side effects, steroid-sparing agents were considered.

Results

IV cladribine IV (0.0875 mg/kg adjusted body weight daily × 4 days at 0, 4, 8, and 16 months) was selected, given its favorable side effect profile including lower risks of malignancy and infertility and the potential for long-lasting effects. The only side effect was short-term fatigue at the time of infusion. At 20 months after cladribine initiation, he was able to wean-off prednisone altogether. Now at 33 months, he remains in clinical and MRI remission.

Discussion

Cladribine is a rational candidate steroid-sparing treatment for presumed neurologic autoimmune conditions such as CLIPPERS.

Classification of Evidence

This study provides Class IV evidence that cladribine is a steroid-sparing treatment consideration in CLIPPERS.

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 **Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
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Case Presentation

A 25-year-old man presented to the emergency department with a reduced level of consciousness after a fall. Four months prior, he experienced intensifying headaches, episodic vertigo lasting seconds, and polydipsia consuming 5L of fluids daily. One month prior, the vertiginous paroxysms worsened in frequency, duration, and severity, lasting several hours, and were associated with vomiting, intractable hiccups, and double vision with left exotropia.

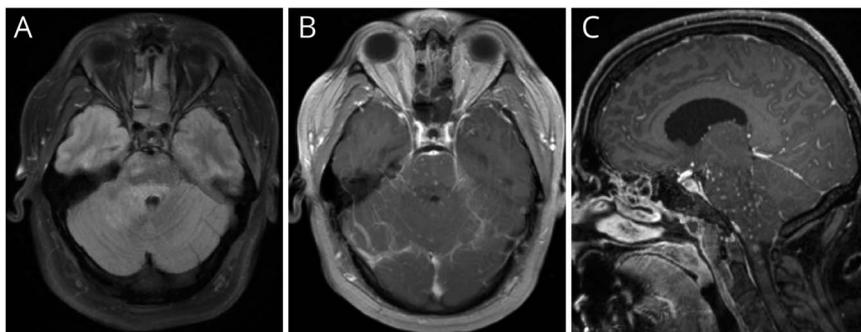
On initial examination, he was hypertensive (190 mm Hg systolic) and had dysarthria, left ptosis, and facial droop. Laboratory testing demonstrated life-threatening hyposmolar hyponatremia (105 mmol/L) and markedly elevated leukocytes (36.1×10^9 cells/L) and CRP (138 $\mu\text{g/mL}$). MRI revealed diffuse serpiginous and nodular enhancement accompanied areas of T2 fluid attenuated inversion recovery (FLAIR) hyperintensity in the midbrain, pons, right cerebellum (Figure 1), and adjacent to the hypothalamus. A lumbar puncture showed mildly elevated protein (0.47g/L), T-cell–predominant lymphocytic pleocytosis (53 cells per μL) with an elevated CD4:CD8 ratio and no CSF-specific oligoclonal bands. CSF glucose, cytology, and flow cytometry were otherwise normal. Serum antibody screening was negative, including aquaporin-4, myelin oligodendrocyte glycoprotein, glial fibrillary acidic protein, tissue transglutaminase immunoglobulin A, rheumatoid factor, lupus anticoagulant, cardiolipin, double-stranded DNA, and antinuclear and anti-neutrophil cytoplasmic antibodies.

Due to progressive obtundation and respiratory compromise within hours of presentation, he was intubated. He completed empiric treatment for an infectious cause of encephalitis; however, blood cultures, sputum cultures, cardiac ultrasound, and serologies for syphilis, Legionella, West Nile, HSV, HIV, VZV, and hepatitis B/C were negative. Toxicology was negative. With concern for an autoimmune process, he received a 3-day pulse of methylprednisolone 1g/d followed by prednisone 80 mg/d. His clinical condition rapidly improved, and he was extubated and transferred to the ward on Day 3 of hospitalization. The

hyponatremia corrected over 4 days. Follow-up imaging on Day 7 showed reduced abnormal T2 FLAIR hyperintensity and enhancement (Figure 2). A prednisone taper (10 mg week) was initiated. Neurologic deficits progressively improved, although there were persistent bilateral VI nerve palsies at discharge on day 13. The eye findings persisted on 1-month outpatient follow-up. Given the presentation with a steroid-responsive lymphocytosis and perivascular pontine involvement, CLIPPER syndrome was favored, although hypothalamic involvement driving hyponatremia and abrupt level of consciousness change was appreciated to be unusual. Neurosarcoidosis was also considered but not supported by the absence of systemic activity after CT screen of the chest/abdomen/pelvis.

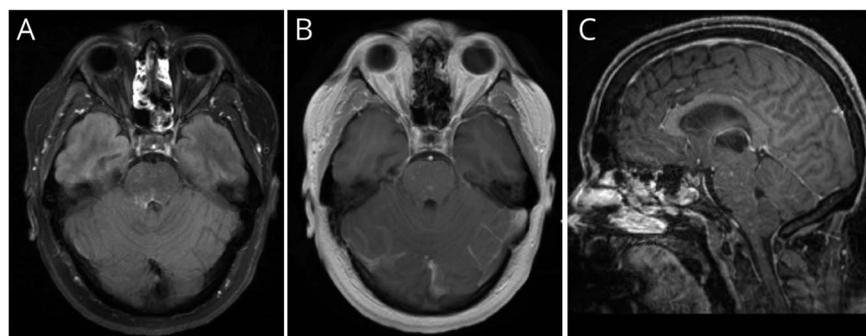
Unfortunately, 2 attempts to wean prednisone lower than 30 mg daily at 6 months and 1 year after diagnosis resulted in worsening of diplopia, at which point MRI scans were repeated, demonstrating persistent gadolinium enhancement similar to the initial presentation depicted in Figure 1. Over this time, steroid side effects had become incapacitating with marked weight gain of more than 50 kg, impaired glucose tolerance, low bone density, tremor interfering with writing, and anxiety so severe that he had to interrupt his studies. Having demonstrated a risk of relapse with steroid taper, steroid-sparing agents were considered including cyclophosphamide and cladribine. Based on the more favorable side effect profile including lower risks of malignancy and infertility and the potential for a long-lasting effect, cladribine was chosen through shared decision-making. Each cladribine treatment cycle consisted of 0.0875 mg/kg of IV cladribine infused over 2 hours on 4 consecutive days. He received a total of 4 cycles at 0, 4, 8, and 16 months. The only reported side effect was short-term fatigue in the days after the infusion. He remained on shingles prophylaxis for the full course of his treatments. MRI scans at 6, 12, 18, and 32 months and clinical visits at similar intervals after initiating cladribine have demonstrated no ongoing enhancement or diplopia. The patient completely weaned-off prednisone by 20 months. At the time of this submission, 33 months since cladribine initiation and off all treatments for more than 1 year, his CLIPPERS remains in clinical and radiographic

Figure 1 Brainstem and Cerebellar MRI Hyperintensities and Punctate Enhancement at First Presentation



Pontine and cerebellar hyperintensities (A, axial T2-weighted FLAIR sequence) with a perivascular pattern of punctate enhancement (B, axial T1 post gadolinium contrast), extending into the medulla and midbrain (C, parasagittal T1 post gadolinium contrast).

Figure 2 Repeat MRI on Day 7 After Presentation Showed Improvements in Abnormalities After Steroids



Following initiation of steroids, there were improvements in the pontine and cerebellar hyperintensities (A, axial T2-weighted FLAIR sequence) and perivascular pattern of punctate enhancement (B, axial T1 post gadolinium contrast; C, parasagittal T1 post gadolinium contrast).

remission. Despite modest weight loss, he remains clinically obese with impaired glucose tolerance. He had completed his Bar examinations and was looking forward to starting his career as a lawyer.

Discussion

Although steroid responsiveness is a defining characteristic of CLIPPERS,¹ protracted corticosteroid courses are often necessary to maintain remission. Attempts to taper steroids below 10–20 mg prednisone often result in clinical and/or radiographic relapse.² To mitigate the risk of long-term exposure, steroid-sparing agents may be used in refractory cases. Although high quality or controlled studies are lacking, effectiveness has been demonstrated for methotrexate, azathioprine, and cyclophosphamide.² Mycophenolate mofetil, rituximab, mitoxantrone, interferon beta-1a,³ tocilizumab,⁴ and leflunomide⁵ have also been used.

Cladribine is a purine (adenosine) analog that selectively promotes apoptosis of T and B lymphocytes with some evidence of broader effect on myeloid cells.^{6,7} As an established disease modifying treatment in MS, cladribine is well tolerated. Contraindications include pregnancy, active malignancy, or infection, and common side effects fortunately not experienced by our patient include lymphopenia, infections, and headache.⁸ The dose and schedule administered was based on our experience using IV cladribine to treat relapsing remitting MS at a dose that is approximately bioequivalent to oral cladribine.

We report a case of CLIPPERS treated with cladribine, which has resulted in nearly 3 years of remission. This treatment represents a rational treatment option worthy of further investigation.

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Disclosure

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Mark S. Freedman, MD	The Ottawa Hospital and University of Ottawa, ON	Study concept or design; analysis or interpretation of data
John Brooks, MD	The Ottawa Hospital and University of Ottawa, ON	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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