Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)

Sean J. Pittock,1,2 Jan Debruyne,3 Karl N. Krecke,4 Caterina Giannini,2 Jelle van den Ameele,3 Veerle De Herdt,3 Andrew McKeon,1,2 Robert D. Fealey,1 Brian G. Weinshenker,1 Allen J. Aksamit,1 Bruce R. Krueger,1 Elizabeth A. Shuster5 and B. Mark Keegan1

1 Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA
2 Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA
3 Department of Neurology, Ghent University Hospital, Ghent, B-9000, Belgium
4 Department of Radiology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA
5 Department of Neurology, Mayo Clinic College of Medicine, Jacksonville, FL 32224, USA

Correspondence to: Dr B. Mark Keegan,
Department of Neurology,
Mayo Clinic College of Medicine,
200 First St. SW Rochester,
MN 55905, USA
E-mail: keegan.bmark@mayo.edu

The classification and pathological mechanisms of many central nervous system inflammatory diseases remain uncertain. In this article we report eight patients with a clinically and radiologically distinct pontine-predominant encephalomyelitis we have named ‘chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids’ (CLIPPERS). The patients were assessed clinically, radiologically and pathologically at Mayo Clinic, USA and Ghent University Hospital, Belgium from 1999 to 2009. Median follow-up duration from clinical onset was 22 months (range 7–144 months). Patients underwent extensive laboratory (serum and cerebrospinal fluid), radiological and pathological testing (conjunctival, transbronchial and brain biopsies) to search for causes of an inflammatory central nervous system disorder. All eight patients (five female, three male) presented with episodic diplopia or facial paresthesias with subsequent brainstem and occasionally myelopathic symptoms and had a favourable initial response to high dose glucocorticosteroids. All patients had symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain and occasionally spinal cord. Radiological improvement accompanied clinical response to glucocorticosteroids. Patients routinely worsened following glucocorticosteroid taper and required chronic glucocorticosteroid or other immunosuppressive therapy. Neuropathology of biopsy material from four patients demonstrated white matter perivascular, predominantly T lymphocytic, infiltrate without granulomas, infection, lymphoma or vasculitis. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids is a definable, chronic inflammatory central nervous system disorder amenable to immunosuppressive treatment. The T cell predominant inflammatory pathology in affected central nervous system lesions and the clinical and radiological response to immunosuppressive therapies is consistent with an immune-mediated process.

Keywords: brain stem; neuroinflammation; encephalitis

Abbreviations: CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
Introduction

The immunopathogeneses of most inflammatory CNS disorders, including those with and without accompanying demyelination, remain poorly understood (Kalman, 2008). Advances in clinical, radiological, serological and pathological evaluation have facilitated disease classification and differentiation of distinctive disease entities (Kalman, 2008). Examples include: (i) revised diagnostic criteria for multiple sclerosis (Polman et al., 2005; based on clinical and radiological data and supportive paraclinical investigations importantly with ‘no better explanation’); (ii) novel autoantibody markers of autoimmune optic neuritis and myelitis [aquaporin-4-immunoglobulin G (IgG) (Lennon et al., 2005; Wingerchuk et al., 2007); collapsin response mediator protein (CRMP-5-IgG) (Cross et al., 2003; Keegan et al., 2008)] and encephalitis [voltage gated potassium channel (Tan et al., 2008) Ma (Dalmay et al., 2004) and NMDA receptor antibodies (Dalmay et al., 2008)] and (iii) immunopathological characterization of neuromyelitis optica [i.e. loss of aquaporin-4 immunoreactivity, vasculocentric distribution of immunoglobulin deposition and complement activation (Roemer et al., 2007)]. We report clinical, radiological and pathological features of a treatable, brainstem-predominant, clinical and radiological entity, which we term chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS).

Patients and methods

The study was approved by Mayo Clinic Institutional Review Board. The 8 patients were assessed clinically, radiologically and pathologically at Mayo Clinic (n=6) (Rochester, MN and Jacksonville, FL) and at Ghent University Hospital (n=2) (Ghent, Belgium) from 1999 to 2009. Patients underwent extensive laboratory (serum and cerebrospinal fluid), radiological and pathological testing (conjunctival, transbronchial and brain biopsies) to search for causes of an inflammatory brainstem-predominant CNS disorder.

Autoimmune serological evaluation

Five of six Mayo Clinic patients had serum (n=4) or CSF (n=2) available for neural autoantibody testing including: cation channel antibodies [voltage-gated calcium channels (P/Q-type and N-type), voltage-gated potassium channels and nicotinic acetylcholine receptors (muscle-type and ganglionic-type)]; skeletal muscle striational antibodies; anti-neuronal nuclear autoantibodies types 1, 2 and 3; Purkinje-cell cytoplasmic autoantibodies types 1, 2 and Tr; anti-glial/neuronal nuclear antibody type 1; collapsin response-mediator protein-5 IgG; amphiphysin IgG and glutamic acid decarboxylase and thyroid autoantibodies. Testing for potential novel or unclassified neural-specific autoantibodies was also performed blinded in a routine clinical laboratory setting using a composite 4 µm frozen section of mouse cerebellum and brainstem, gut and kidney (standardized to detect paraneoplastic autoimmunity) (Pitcock et al., 2006). To minimize interference by non-neuronal-specific antibodies, sera were preabsorbed (at 1:240 dilution) with bovine liver powder. Fluorescein-conjugated goat anti-human IgG (Southern Biotechnology; Birmingham, AL) detected bound IgG.

Imaging

Brain MRI was performed in 1.5 T MRI scanners, and images from T1 (pre and post administration of gadolinium), T2 fluid attenuation inversion recovery and proton density sequences were acquired. A median of five MRIs (range 3–12) per patient were available for review, spanning a median interval of six months (range 1–104 months) and including pre and post therapy images. Vascular neuroimaging was available for review in four patients, specifically magnetic resonance angiography (n=2) and conventional cerebral angiography (n=2). Spinal cord MRI exams with gadolinium were available for five patients. All patients underwent chest CT imaging to address the possibility of sarcoidosis, and three patients also had CT examination of abdomen and pelvis.

Pathological methods

Three patients underwent brain biopsy at Mayo Clinic (Patients 1, 2 and 5) and one at Ghent University Hospital (Patient 6). Tissue slides were made from formalin fixed paraffin embedded brain specimens and stained with haematoxylin and eosin, luxol fast blue counterstained with periodic acid-Schiff and silver impregnations (modified Bielschowsky). Immunohistochemical stains obtained included glial fibrillary acid protein for astrocytes (clone GA5, 1/1,000; BioGenex), CD68 (clone KP-1, 1/200 dilution; Dako) for microglia/macrophages, CD3, CD1a, CD20, CD117 and placental alkaline phosphatase.

Results

Clinical characteristics

Symptoms

The clinical characteristics of the eight patients (median age at onset 45.5 years; range 16–86 years; five females and three males) are shown in the Table 1. All patients had subacute gait ataxia and diplopia. Seven patients also developed dysarthria (primarily ataxic but with some spastic features). An altered sensation or tingling of the face or scalp was reported by five of eight patients. Other symptoms included non-specific dizziness, nausea, dysgeusia, pseudobulbar affect (pathological crying or laughter), tinnitus, tremor, nystagmus, paraparesis, sensory loss and spasticity. None had significant systemic symptoms nor weight loss, fever, meningism, lymphadenopathy, polydipsia/polyuria or other symptoms of hypothalamic dysfunction, uveitis or oral and/or genital ulcers.

Neuroimaging

Brain MRI in all eight patients revealed a characteristic pattern of punctate and curvilinear enhancement peppering the pons (Fig. 1) and extending variably into the medulla, brachium pontis and mid-brain. A subtler radiating pattern of similar enhancing lesions extended into the basal ganglia and inferior cerebellar white matter in three patients, corpus callosum in one patient and spinal cord in three patients (Fig. 2). Lesions were typically less numerous and smaller as distance from the pons increased. The largest single punctate lesion was 9 mm in greatest dimension, but most lesions measured between 1 and 3 mm. One patient presented with asymmetric enhancement in the left pons and right
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at onset (years)</th>
<th>Duration of follow-up (months)</th>
<th>Symptoms at onset</th>
<th>Symptoms during illness evolution</th>
<th>Location of perivascular contrast enhancement on MRI</th>
<th>CSF abnormalities</th>
<th>Time from onset to brain biopsy (months)</th>
<th>Time from onset to glucocorticosteroid therapy (months)</th>
<th>Initial dose, route and response to glucocorticosteroids</th>
<th>Maintenance treatment and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>78</td>
<td>20</td>
<td>Ataxia, diplopia</td>
<td>Ataxic dysarthria, diplopia, altered facial sensation, action tremor, pseudobulbar affect (pathological crying), palatal myoclonus</td>
<td>Symmetric in medulla, pons (brachium pontis), midbrain and basal ganglia</td>
<td>10 white blood cells, protein↑, NSE↑</td>
<td>9</td>
<td>12</td>
<td>Prednisone 80 mg daily: radiological improvement without marked clinical improvement</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>37</td>
<td>144</td>
<td>Episodic facial tingling</td>
<td>Ataxia, spastic ataxic dysarthria, diplopia, pseudobulbar affect (pathological laughter), nausea, dizziness, neurogenic bladder</td>
<td>Symmetric in medulla, pons, inferior and superior cerebellar peduncles. Upper cervical spinal cord involvement</td>
<td>Protein↑, OCB↑</td>
<td>36</td>
<td>4</td>
<td>1 g IVMP daily for 5 days; dramatic improvement</td>
<td>Initially used pulse IVMP and prednisone taper for first few years then combined oral prednisone and methotrexate. Patient now stable on methotrexate monotherapy</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47</td>
<td>7</td>
<td>Episodic horizontal diplopia</td>
<td>Ataxia, ataxic dysarthria, diplopia, altered scalp and limb sensation, dysphagia, spells (lasting seconds) of speech arrest and leg stiffening</td>
<td>Symmetric paramedian midbrain, pons, cerebellar peduncles</td>
<td>Biopsy not done</td>
<td>5</td>
<td>5</td>
<td>1 g IVMP daily for 5 days: moderate improvement</td>
<td>Oral prednisone</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>86</td>
<td>25</td>
<td>Horizontal diplopia</td>
<td>Ataxia, ataxic dysarthria, diplopia, altered facial sensation, dizziness, intermittent lightheadedness</td>
<td>Symmetric mid brain (left cerebral peduncle), pons and extending minimally into the middle cerebellar peduncles</td>
<td>OCB↑, NSE↑</td>
<td>Biopsy not done</td>
<td>7</td>
<td>1 g IVMP daily for 5 days: dramatic improvement</td>
<td>1 g IVMP every 10-14 days: died 16 months later from pulmonary embolus</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>70</td>
<td>22</td>
<td>Horizontal diplopia</td>
<td>Ataxia, ataxic dysarthria, altered facial and limb sensation, nausea, fatigue, tinnitus, tongue weakness</td>
<td>Symmetric dorsal medulla, pons and midbrain</td>
<td>Protein↑</td>
<td>20</td>
<td>21</td>
<td>1 g IVMP daily for 5 days: moderate improvement</td>
<td>Oral prednisone 60 mg for three months tapering by 10 mg every two weeks</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>41</td>
<td>14</td>
<td>Diplopia</td>
<td>Ataxia, ataxic dysarthria, dizziness.</td>
<td>Cerebellar peduncles right greater than left, pons</td>
<td>Initial↑ OCB then OCB normalized on repeat CSF Normal</td>
<td>13</td>
<td>1</td>
<td>IVMP; resolution within 2 weeks</td>
<td>Initiated mitoxantrone in addition to glucocorticosteroids.</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>16</td>
<td>43</td>
<td>Diplopia</td>
<td>Ataxia, paraparesis, diplopia, vertical upbeat nystagmus</td>
<td>Symmetric pons, cerebellum, midbrain. Cervical and thoracic spinal cord involvement</td>
<td>Biopsy not done</td>
<td>1</td>
<td>1</td>
<td>1 g IVMP daily for 5 days with oral prednisone taper for 2 weeks; complete resolution of brainstem symptoms</td>
<td>Worsened following glucocorticosteroid taper. Azathioprine added later to glucocorticosteroids did not control recurrence</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>44</td>
<td>7</td>
<td>Horizontal diplopia</td>
<td>Ataxia, dysarthria, dysgeusia, paraparesis, hyperacusis</td>
<td>Symmetric pons, cerebellum, midbrain. Cervical and thoracic spinal cord involvement</td>
<td>Protein↑</td>
<td>Biopsy not done</td>
<td>3</td>
<td>1 g IVMP daily for 5 days with oral prednisone taper for 2 weeks; dramatic improvement</td>
<td>Reinitiated prednisone tapers.</td>
</tr>
</tbody>
</table>

NSE = neuron specific enolase; OCB-CSF = unique oligoclonal bands; IVMP = intravenous methylprednisolone; M = male; F = female; ↑ = elevated.
mesencephalon that progressed over 6 months to become more extensive and symmetric (Fig. 3). Cervical and thoracic spinal cord MRI performed with and without contrast was normal in two patients, and in three patients showed foci of punctate gadolinium enhancement within the spinal cord (Fig. 2). There were no other remote supratentorial parenchymal white or grey matter enhancing lesions, no hypothalamic-pituitary involvement and no bony, meningeal or pial lesions. There was patchy non-specific increased T2 signal in the corresponding regions of gadolinium enhancement. None of the lesions had significant mass effect.

Intracranial magnetic resonance angiography performed in two patients and conventional angiography of neck and intracranial vessels in two other patients were normal without angiographic evidence of vasculitis.

Differential diagnoses

Diagnoses considered included: neurosarcoidosis, CNS lymphoma, lymphomatoid granulomatosis, CNS vasculitis, Bickerstaff brainstem encephalitis, paraneoplastic disease, chronic perivascular infectious process (tuberculosis, neurosarcoidosis, Whipple’s disease, parasitic infection), glioma, CNS demyelinating disease, CNS Behçet’s and histiocytosis including Langerhans cell histiocytosis and Erdheim-Chester disease.

Laboratory investigations

Extensive systemic work-up included: complete blood count; renal and liver function (all values normal in eight patients tested); sedimentation rate (normal in four tested); angiotensin converting enzyme (one of seven patients tested had an elevated value of 74 U/l; normal range 7–46 U/l); anti-nuclear antibody [one of six tested was seropositive (4.8 U; normal <1 U; double stranded DNA antibody was negative)]; antibodies against extractable nuclear antigens [negative in three tested; Sjögren syndrome B (SSB) minimally elevated in one (value 1.1 U; normal <1.0 U who was anti-nuclear antibody negative)]; and viral, fungal and syphilis serologies (negative in eight tested). Radiological investigations negative in all patients were: CT chest (all eight patients), CT abdomen and pelvis (three patients), whole body PET (two patients), testicular ultrasound (two patients) and mammogram (two patients).

No neural specific IgGs were identified in the five patients (sera n = 4, CSF n = 2) tested. Serum antibodies against the aquaporin-4 water channel (neuromyelitis optica immunoglobulin G; NMO-IgG) were assessed and negative in 4 Mayo Clinic patients and one patient whose CSF was tested. One Belgian patient’s serum (Patient 7) tested was NMO-IgG negative. Pathological investigations other than brain biopsy included: conjunctival biopsy in three patients and transbronchial lung biopsy in 1, all of which yielded normal tissue.

Electrophysiological assessments done and normal were visual evoked response (n = 2), brainstem auditory evoked response (n = 2) and somatosensory evoked potentials (n = 1).

Cerebrospinal fluid analyses

CSF abnormalities were found in four of eight patients tested: mildly elevated protein in four (47–65 mg dl−1; normal reference range 15–45 mg dl−1), and pleocytosis in 1 (10 white blood cells ul−1, 98% lymphocytes). Elevated unique CSF oligoclonal bands were found in three of six tested, including one patient whose electrophoretic pattern reverted to normal. CSF cytology
with flow cytometry was negative for malignant cells in all eight patients. Fungal cultures (7) and *Tropheryma whippelii* polymerase chain reaction (2) were also negative.

### Neuropathology

Sites chosen for brain biopsies in four of eight patients were the pons in one and cerebellum in three. The biopsy findings were similar in each case and revealed a marked lymphocytic infiltrate in the white matter with perivascular predominance, but also a more diffuse parenchymal inflammatory infiltrate (Fig. 4). The lymphocytic infiltrate was composed predominantly of CD3 reactive T lymphocytes and some CD20 positive B lymphocytes. CD68 positive histiocytes and activated microglia were present in moderate number. Myelin was intact. Special stains for fungi and mycobacteria (Grocott methenamine silver and auramine rhodamine) were negative. Characteristic findings of sarcoidosis, histiocytosis, lymphoma, lymphomatoid granulomatosis, multiple sclerosis or other diseases were not found.

### Treatment

All patients were treated initially with glucocorticosteroids [intravenous methylprednisolone (1 g daily for 5 days) in seven and oral prednisone (80 mg daily) in one]. The median time from symptom onset to glucocorticosteroid treatment initiation was 6.75 months (range 1–21 months). All seven patients treated with intravenous methylprednisolone showed improvements in gait, diplopia, head and limb sensation and dysarthria between Days 2 and 4 of treatment. Patient 1 treated with 80 mg oral prednisone did not experience clinical improvement. The number and size of perivascular enhancing lesions was reduced on post-treatment MRI exams in all patients (Fig. 5). Lesion distribution continued to be concentrated in the pons. Long-term therapeutic response varied, ranging from excellent (Patient 2) to incomplete with ongoing inflammatory disease despite immunosuppressive medications (Patient 6).

All treated patients required maintenance immunosuppression to sustain clinical improvements (Table 1). In 6 cases in which withdrawal or reduction of glucocorticosteroids was attempted, clinical relapse ensued.

### Illustrative case history—Patient 2

Two years prior to evaluation at Mayo Clinic, the patient noticed episodic facial tingling but was well otherwise. Six months prior, he developed painless, horizontal, binocular diplopia and subsequently gait ataxia, worsening over 2 months. Brain MRI showed brainstem gadolinium enhancing abnormalities centred within the pons. Serological investigations were normal and CSF demonstrated elevated unique oligoclonal bands. He was treated for five consecutive days with 1000 mg intravenous methylprednisolone and his symptoms improved. Further investigations were unrevealing. He remained in clinical remission without ongoing treatment for 1 year, after which he experienced worsening gait ataxia, dysarthria and recurrent horizontal diplopia. Repeat brain MRI demonstrated enlarging areas of gadolinium enhancing lesions within the brainstem (Fig. 5A). A pontine biopsy was performed while on no therapy (Fig. 4D–F). He was retreated with five consecutive days of 1000 mg intravenous methylprednisolone and he again had marked symptomatic improvement. He then had three more similar episodes of symptomatic worsening within the following 8 months that all reliably improved with intravenous corticosteroids, only to relapse following their discontinuation. Chronic therapy with oral prednisone 60 mg every other day was therefore initiated and he experienced steady improvement.
in diplopia, dysarthria, gait ataxia and dysphagia. Brain MRI showed significant improvement in the gadolinium enhancing lesions (Fig. 5B).

Oral hydroxychloroquine (400 mg daily) was introduced and prednisone was weaned over months because of glucocorticosteroid side effects. Six months later, brain MRI showed radiological progression of the inflammatory lesions (Fig. 5C) although clinically he remained stable. Following reinitiation of oral prednisone (60 mg every other day), a follow-up brain MRI scan showed improvement, the hydroxychloroquine was discontinued and oral methotrexate (7.5 mg once weekly) was started and gradually increased to 20 mg weekly.

After 1.5 years of clinical and radiological stability on methotrexate and prednisone, alternate day treatment with oral prednisone was reduced by 5 mg each month and at last follow-up he remained on oral methotrexate (10 mg weekly) monotherapy without radiological recurrence (Fig. 5D). He has developed neither symptoms or radiological evidence of other CNS diseases such as multiple sclerosis nor a systemic disease despite follow-up of 12 years.

Discussion

We suggest that the constellation of clinical, radiological and pathological findings reported in these eight patients represents a definable, treatable inflammatory CNS, brainstem-predominant syndrome (CLIPPERS). Clinical and radiological findings point to a pontine-centric disorder with variable involvement of adjacent structures. All patients experienced cranial sensory abnormalities, diplopia, ataxia and dysarthria, and had a signature MRI punctate pattern of patchy gadolinium enhancement ‘peppering’ the pons, brainstem, cerebellum and spinal cord. Neuropathology in four of eight patients revealed a prominent perivascular lymphocytic infiltrate. Immunosuppressive therapy was successful in improving clinical symptoms and radiological disease; however, early glucocorticoid taper was accompanied by recurrence of both symptoms and radiological progression, and therefore prolonged therapy appears to be necessary for the majority of cases.

Other disorders likely to present with these findings were carefully excluded. Neurosarcoidosis (Spencer et al., 2005; Brown et al., 2008), CNS lymphoma (Batchelor and Loeffler, 2006) and CNS vasculitis (Salvarani et al., 2007; Miller et al., 2009) were the three alternative diagnoses most strongly favoured in the initial evaluation. Although not characteristic, each of these entities could show a similar pattern of perivascular or infiltrative gadolinium enhancement on MRI. Pathological review of lung, conjunctival or brain biopsy tissues failed to reveal non-necrotizing granulomas with giant cells typical of sarcoidosis. CSF cytology, systemic imaging, hematologic investigations and neuropathology revealed no evidence of lymphoma. Vasculitis was not found on conventional or magnetic resonance angiography, and pathology showed no partial or transmural destructive vascular inflammation involving leptomeningeal or parenchymal vessels (Miller et al., 2009) in biopsy specimens.
Figure 4 Neuropathology from Patients 1, 2, and 5. Marked perivascular and parenchymal lymphocytic infiltrates in the white matter (haematoxylin and eosin stain), for Patients 1 (A × 100, B × 200), 2 (D × 40, E × 200), and 5 (G × 100). The lymphocytic infiltrate was composed predominantly of CD3 positive (T) lymphocytes in all cases (Patient 1, C × 400; Patient 2, F × 400; Patient 5, H × 200); similar pathology was demonstrated in Patient 6 (results not shown).
Other diagnoses considered but excluded were: histiocytosis X (Prayer et al., 2004; Langerhans cells were absent and neuroimaging was inconsistent), paraneoplastic disease (Ellison et al., 2008; systemic workup for malignancy, paraneoplastic autoantibody markers were negative and neuropathology lacked characteristic microglial nodules and neuronophagia), demyelinating disease (Lucchinetti et al., 2008; no evidence of demyelination on pathology, nor were there typical MRI findings). The clinical course, negative microbiology workup, improvement with immunosuppressants and absence of well-formed microglial nodules, necrotizing granulomata or stainable microorganisms argue strongly against infectious processes.

Bickerstaff brainstem encephalitis deserves particular attention, as it is also a brainstem-predominant inflammatory disease. This diagnosis was excluded in these patients by the observed neuropathology and radiological features and lack of peripheral nerve involvement (Odaka et al., 2003; Ito et al., 2008). Diagnostic features of Bickerstaff brainstem encephalitis include drowsiness or coma, progressive external ophthalmoplegia, ataxia and corticospinal tract signs; the vast majority of cases occur following viral illness and have a monophasic course and a good prognosis. MRI abnormalities occur in a minority (10–31%) of patients with Bickerstaff brainstem encephalitis and, when present, typically appear as a homogenous, non-gadolinium enhancing lesion easily differentiated from the pepper-like gadolinium enhancement seen as a hallmark MRI feature in our patients (Chataway et al., 2001; Mondejar et al., 2002). Furthermore, peripheral polyneuropathy and serum anti-ganglioside GQ1b IgG antibodies are present in the majority of patients with Bickerstaff brainstem encephalitis, and thus it is now considered to be in the spectrum of Miller Fisher Guillain Barré syndrome with coexistent CNS involvement.

Although only eight subjects were identified, we suspect that this disorder may be under-recognized, considering the relatively short duration over which these patients were identified in three academic centres. Despite a characteristic clinical and radiological syndrome, other, as yet undefined, aetiologies could present in a similar fashion and perhaps were not excluded in the four patients lacking pathological examination. Those without pathological confirmation seemed to have similar imaging, outcome and radiological response to therapy as those in whom this was accomplished. Although the median duration of follow-up was short (median 20 months), it was reassuring that those patients with the longest follow-up experienced neither dissemination of the disease in the CNS nor any underlying systemic illness nor evidence of idiopathic inflammatory demyelinating disease such as multiple sclerosis despite follow-up as long as 12 years.

Despite the eloquence of the primarily involved CNS region (brainstem, cerebellar peduncles), pathological examination was accomplished in four cases and showed identical pathology that corresponded to the neuroimaging abnormalities noted in all the patients. It remains possible, given the sample size limitations.

Figure 5  Marked reduction in extent of gadolinium enhancement following immunotherapy in Patient 2. Axial T1 MRI brain with gadolinium. (A) At time of relapse, off of all immunosuppressive therapy and prior to brain biopsy. (B) Near complete resolution of gadolinium enhancing lesions following chronic oral prednisone. (C) Recurrent gadolinium enhancing lesions following discontinuation of prednisone. (D) Improvement and stability for over 1.5 years on methotrexate monotherapy.
required to prevent neurological injury, other pathology may have been missed. However, the biopsies were of substantial quality and size for pathological interpretation and there were no cases where the biopsy suggested an alternative pathology, even around the margins of the submitted sample. Extensive evaluations were done in all patients and no alternative diagnoses were found. The clinical course and neuroimaging features were similar between those with and those without tissue pathology, although an alternative pathological process could not be excluded as causing this identical syndrome in patients where pathology was not documented.

The pathogenesis of CLIPPERS is unknown. The presence of a perivascular and parenchymal inflammatory cell infiltrate in affected CNS tissue combined with the clinical response to immunosuppressive therapies suggests an autoimmune or other inflammatory mediated pathogenesis. If organ-specific autoimmunity is its basis, then the location of the inflammatory infiltrate suggests that the target autoantigen is likely to be located in perivascular regions. A limited form of multiple sclerosis is excluded given the lack of development of more typical attacks and MRI lesions and the neuropathological findings.

We recommend full evaluation with both non-invasive and minimally invasive procedures to attempt to make a clear diagnosis if similar cases are encountered. The patients who underwent biopsies did not experience adverse effects of the neurosurgical procedure. Given the location of the prominent abnormalities within the brainstem, however, caution needs to be taken prior to consideration of this in similar cases. Biopsy should be considered in patients when alternative diagnoses remain likely and experienced neurosurgical colleagues recommend that it may be performed safely. Conversely, if alternative diagnoses are rigorously excluded, the clinical and radiological features may be sufficiently distinctive that CLIPPERS could be diagnosed and treated without pathological examination.

Conflict of interest

Dr. Keegan is compensated as a Section Editor for Neurology® and as Chief Editor for eMedicine. The authors report no other conflict of interests.

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