A NEW DEFINED ENTITY AMONG THE SPECTRUM OF CENTRAL NERVOUS SYSTEM INFLAMMATION: CHRONIC LYMPHOCYTIC INFLAMMATION WITH PONTINE PERIVASCULAR ENHANCEMENT RESPONSIVE TO STEROIDS (CLIPPERS)

O. Jerca[1], A. Manouchehrinia[1], R. Tanasescu[1,2]

[1]Division of Clinical Neurology, Queen's Medical Centre, Nottingham, UK
[2]Department of Neurology, Colentina Clinical Hospital, Bucharest, Romania

ABSTRACT

A newly defined CNS inflammatory disease was recently described by Pittock et al. from the Mayo Clinic College of Medicine [1]. They report a series of 8 patients with CNS inflammation with similar clinical, radiological and pathological features, that they named CLIPPERS (Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids). Since then, other few cases have been reported. The aim of this short review is to outline the general characteristics of the newly defined CLIPPERS, as this new entity should be considered by the clinician for the differential diagnosis of central inflammatory disease.

Key words: brainstem lesion, pons, inflammation, perivascular infiltrate, encephalitis, vasculitis, lymphoma, glioma, antibodies

The differential spectrum of inflammatory lesions of the central nervous system is wide, the etiological diagnosis being frequently a challenge for the general neurologist. In this respect, it is mandatory for the clinician to acquire new information on the most recently described pathological entities and to integrate it in the broader spectrum of differentials when facing CNS inflammation.

In 2010, a group of neurologists from Mayo Clinic College of Medicine defined a new clinical, radiological and pathological entity: Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) [1]. In the last 10 years, only 8 patients have been reported with CLIPPERS, but apparently this entity is still under-recognised.

We shall briefly overview the clinical, radiological and pathological features of CLIPPERS, as described in the Mayo group's series of cases, with a special emphasis on the differential diagnosis when confronting mainly with the clinical and radiological picture.

All patients with CLIPPERS in the Mayo's series presented with multiple relapsing focal brainstem signs: diplopia, cerebellar and proprioceptive ataxia, dysarthria, facial hypoesthesia, nystagmus and vertigo, altered limb superficial and deep sensation, with an asymmetrical pattern. Only two patients had a superimposed paraparesis and sphincteric dysfunction.

The median age at onset of the symptoms was 45 years old, with subacute initial multifocal signs. The relapsing pattern manifested by episodic worsening of ataxia, cranial nerve dysfunction and/or spinal cord dysfunction, during the period of follow-up.

Author for correspondence:
R. Tanasescu, MD, Colentina Clinical Hospital, 19-21 Stefan cel Mare Avenue, District 2, Zip Code 020125, Bucharest, Romania
e-mail: Radu.Tanasescu@nottingham.ac.uk

Brain MRI was characteristic in all the 8 reported cases. It revealed a pattern of punctuate gadolinium enhancement at the level of the pons and midbrain. Only in 3 patients, similar punctuate lesions were noticed in the basal ganglia, corpus callosum and in 1 patient at the level of the cervicothoracic spinal cord. The lesions were small in dimensions, around 3 mm each, with no confluent disposition, and centrally distributed at the pontomesencephalic and spinal cord level.

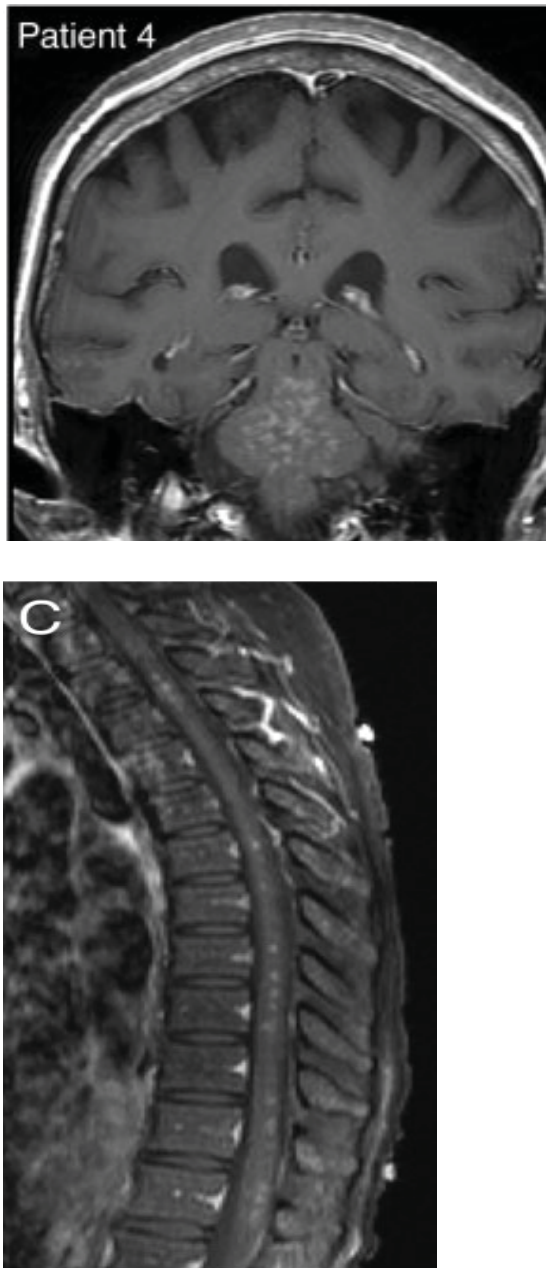

Figure 1. *Punctuate gadolinium enhancing lesions in the midbrain and cervico-thoracic spinal cord; images from different patients (reproduced with permission from [1])*

The brain biopsy, from the affected anatomical areas performed in 4 out of 8 patients confirmed a specific pattern of inflammation. There were lymphocytic infiltrates disposed in the perivascular tissue and also scattered in the white matter inside the parenchyma (haematoxylin – eosin stain). The lymphocytic infiltrate contained numerous T reactive cells with a CD3 phenotype and few B cells, a moderate number of histiocytes CD68 phenotype and activated microglia. There was no aspect of demyelination or intravascular deposits of inflammatory cells, any leptomeningeal deposits or granulomatous infiltration with macrophages. The aspect of biopsy defined a new type of CNS inflammatory disease, with no other already known similar description of the pathological findings.

Diverse laboratory tests were checked by the Mayo group in order to search for causes of other inflammatory CNS disease. Serological inflammatory markers were negative, in view of vasculitis of CNS, either primary or secondary to systemic autoimmune diseases or to chronic infections [2]. A large panel of specific antibodies in search of Antineutrophil Cytoplasmic Autoantibodies (ANCA) associated vasculitides (Wegener's granulomatosis, Churg-Strauss and microscopic polyangiitis) confirmed two borderline values for ANCA [3]. Sjogren syndrome (anti-SSA/Ro, anti-SSB/La) [4], systemic lupus erythematosus (ANCA, dsDNA, anti-Sm) [5] with CNS involvement, were not evidenced in the autoimmune screening. The patients had negative clinical and biological markers for systemic organ dysfunction, like renal, rheumatological, pulmonary, gastro-intestinal, skin, oro-pharyngeal and peripheral nervous system disease. Conjunctival and transbronchial biopsies were negative regarding any inflammatory local infiltrate. Infectious panel for HIV, varicella-zoster virus, herpes simplex virus, cytomegalovirus, B hepatitis, syphilis and tuberculosis was also negative, in view of a possible secondary infectious vasculitis [6].

The aspect of cerebrospinal fluid revealed a mildly increased total protein concentration of 65 mg/dl in 5 out of 8 tests (normal reference of up to 45 mg/dl) and pleocytosis with lymphocyte predominance in 1 case. Oligoclonal bands were tested in 6 patients and returned positive in 3, with 1 case of normal reversion of the bands at a subsequent analysis. No infectious agent or malignant cells were found in CSF. The CSF was highly suggestive for an inflammatory CNS disease with intrathecal production of antibodies due to the presence of oligoclonal bands, for which no specific antigen was found.

Neurosarcoidosis with granulomatous vascular infiltration, cerebral intravascular lymphoma [7]

and low grade glioma [8] might be considered as differentials, but only brain biopsy excluded these entities. Neuro-Behcet's disease with possible brainstem involvement was also excluded by lack of systemic features and ultimately by biopsy [9]. Also rare forms of CNS histiocytosis with brainstem involvement have been described, the biopsy from infiltrated regions clarifying the diagnosis [10].

The Mayo group considered as differentials also conditions known to produce focalised types of CNS demyelination, like neuromyelitis optica and encephalitis of diverse aetiologies, paraneoplasic, autoimmune (Bickerstaff brainstem encephalitis) or primary infectious. A serological screening was negative for aquaporin 4 water channel antibodies, potassium channel antibodies and several types of paraneoplasic antibodies. The chest and abdominal tomography, pelvic ultrasound, mammography and one PET scan in a single case excluded globally a primary malignancy. The autoimmune variant of brainstem encephalitis with or without multiple extra-pontine demyelinative lesions has particular association with autoimmune neuropathies, like Guillain-Barre or Miller-Fisher type of ophtalmoplegia and ataxia, with positive anti-ganglioside GQ1b antibodies, being considered a combined autoimmune central and peripheral nervous system disease [11], [12].

The relapsing clinical outcome in certain patients could be explained by outburst of inflammatory infiltrate through an altered brain barrier that did not cause demyelination, because the myelin was intact in the pathological study. This lymphocytic inflammation was based on certain cell phenotype, but what triggers this special type of inflammation is not known at present. Larger studies are warranted in the future.

Seven out of 8 patients had an excellent immediate clinical response to steroids, 1 g/day IV methyprednisolone for 5 days, from the beginning of treatment. Only 1 patient who received oral Prednisone 1 mg/kg from the disease onset did not experience clinical improvement. Nevertheless, serial cerebral and spinal MRIs performed subsequently after the treatment showed a reduction in the number of punctuate lesions and even a clear disappearance of some lesions. Long-term therapeutic response was variable related to steroids tapering. Three patients received long-term treatment with other immunosuppressants, like methotrexate, mitoxantrone and azathioprine, due to recurrences of neurological symptoms, related mostly to spinal cord involvement. The attempts to withdraw the steroid treatment facilitated a rebound of the clinical and also of the confirmed MRI activity in 6 patients.

Very recently, another case of a patient fulfilling CLIPPERS criteria but with initial normal MRI has been reported by a French group [13]. Interestingly, the 46-year-old patient presented with a relapsing symptomatology of brainstem involvement starting at the age of 13 years, with recurrent attacks responsive to steroids in the following 30 years. The MRI showed abnormalities only after 9 years from the onset, suggesting that serial MRI examinations may be necessary when a diagnosis of CLIPPERS is suspected. The brain biopsy finally added the definite support for a similar pattern of CNS perivascular lymphocytic inflammation as in the newly defined CLIPPERS. Some controversies exist on possible meningeal involvement in CLIPPERS [14]. However, the T cell predominant inflammatory pathology and the clinical and radiological response to immunosuppressive therapies are concordant with an immune-mediated process in all cases described.

The two latest reports of a highly suspected cases of CLIPPERS have been published in the March issue of Brain, this year [15, 16]. List et al. describe a gradually worsening brainstem syndrome, with similar characteristic MRI pattern, reversal of oligoclonal bands at repeated lumbar puncture and a good response to IV and oral tapered steroids. The initial positivity of oligoclonal bands and subsequent negativation are specific for a dynamic immune mediated CNS disorder. No biopsy was performed, possibly due to previous novel defined pathological findings by the Mayo group and their preliminary recommendations of therapy [15].

Contrast-enhanced magnetic resonance monitoring and perfusion-weighted findings can add significant information and act as 'safety nets', as recently was showed by Duprez and Sindic [16]. They report a case in which the severity of pontine inflammation was extreme and unequalled when compared with images from the Mayo's group, being followed by rapid atrophy leading to severe parenchymal shrinkage of the pons [16]. The authors noted that, in spite of intense treatment resulting in significant clinical improvement, contrast enhancement remained and perfusion-weighted imaging showed persistent increase in regional cerebral blood flow values. These unexpected findings were interpreted by Duprez et al. "as resulting from persistent leakage of contrast agent molecules through unrepaired blood-brain barrier of capillaries enlarged by a post-inflammatory 'vasoplegic' status" [16].

Performing a high quality brain biopsy, which is an invasive technique, poses often logistical difficulties in general neurological practice. In this respect, careful differential diagnosis of recurrent inflammatory CNS conditions is mandatory (Table 1). In front of a patient with brainstem or spinal cord relapsing symptoms and a highly suggestive MRI pattern, CLIPPERS might be considered and a full evaluation including non-invasive and minimally invasive procedures should be performed. CLIPPERS is still an exclusion diagnosis, but treatment can be initiated without pathological examination if careful analysis of the clinical and radiological context are highly suggestive for this newly defined pathogenic entity.

Table 1. *Differential diagnosis of brainstem multifocal heterogeneous lesion with and/or without other CNS involvement (modified after [17])*

Disease Entity	Clinical signs	MRI pattern	Serological immune screening / CSF study	Brain biopsy	Treatment
Primary medium and small vessel vasculitis of CNS	Headache, encephalopathy, multifocal neurological signs, Peripheral neuropathy Relapsing pattern Systemic features, target organ involvement	Multifocal vascular lesions of different ages +/- intracerebral haemorrhage +/- leptomeningeal enhancement Angiography-specific findings	Systemic inflammatory syndrome ANCA antibodies Other autoimmune antibodies	Intravascular lymphocytic infiltrate Amyloid deposition Granulomatous infiltrate and immune complex deposition Necrosis of vessel wall	Steroids Other immune-suppressants
Vasculitis secondary to connective tissue disease	Focal neurological signs, peripheral neuropathy Encephalopathy Weight loss, fever Systemic target organ involvement	Multifocal vascular pattern	Typical serological antibodies target organ biological impairment	Usually not necessary	Immuno-suppressants Monoclonal antibodies
Vasculitis secondary to infections	Fever, skin reaction Focal neurological signs Encephalopathy	Vascular pattern +/- meningeal enhancement	Serum antibodies specific for antigen type CSF - elevated prot. + cells CSF - positive culture	Complex immune deposition and positive antigen mononuclear cells intra and perivascular	Antiviral and antibacterial agents Steroids in selected cases
Neuro-Behcet	Oral and genital ulcers Arthritis Headache Focal neurological signs Meningo-encephalitis	Confluent brainstem lesion Other CNS involvement	HLA-B51 in 20% Europeans No specific serological markers	Intense perivascular inflammatory infiltrate with different cells type	Steroids Other immuno-suppressants Anti-TNF agonists (Infliximab)
Neuro-myelitis optica	Optic neuritis Myelitis, usually severe Rarely, vomiting, hiccups (brainstem involvement)	Extensive spinal lesion Optic neuritis Brainstem lesion – rare	Anti-NMO antibodies	Usually, unnecessary for diagnosis	Steroids Immuno-globulin Plasmapheresis Immuno-suppressors Monoclonal antibodies (Rituximab)
Bickerstaff brainstem encephalitis	Encephalopathy Ophtalmoplegia Ataxia Peripheral neuropathy with areflexia	Focal brainstem +/- CNS lesions	Anti-GQ1b Anti-GM1 antibodies CSF-albumino-citological dissociation	Perivascular lymphocytic infiltrate with demyelination	Immuno-globulin Plasmapheresis
Low grade glioma	Focal progressive neurological signs	Heterogeneous brainstem lesion	Chromosomial abnormalities	Diagnostic test for histological classification	Surgery Radiation Immuno-therapy

Disease Entity	Clinical signs	MRI pattern	Serological immune screening / CSF study	Brain biopsy	Treatment
Histiocytosis	Focal neurological signs	Focal lesion, cerebellum and pons, usually confluent	Non-specific	Diagnostic test Perivascular histiocytes, gliosis	Surgery Chemotherapy Radiotherapy
CNS intra-vascular lymphoma	Focal neurological progressive signs Fever Skin rash Encephalopathy	Linear, punctuate, patchy enhancement lesions +/- meningeal enhancement	Non-specific	Diagnostic test Intravascular neoplasic lymphocytes, usually B-cells	Chemotherapy Radiotherapy
Para-neoplasic brainstem encephalitis	Encephalopathy Focal neurological signs	Usually confluent lesion	Anti-neuron antibodies	Not necessary	Treatment of the primary tumour Plasmapheresis Immuno-globulins

REFERENCES

1. **S.J. Pittock, et al.** – Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *Brain* 2010. 133(9):2626-2634
2. **C.A. Langford** – Vasculitis. *J Allergy Clin Immunol*, 2010; 125(2 Suppl 2):S216-225
3. **J.U. Holle, W.L.** – Gross, Neurological involvement in Wegener's granulomatosis. *Curr Opin Rheumatol* 2011; 23(1):7-11
4. **B. Segal, A. Carpenter, D. Walk** – Involvement of nervous system pathways in primary Sjogren's syndrome. *Rheum Dis Clin North Am* 2008; 34(4):885-906, viii
5. **P. Cieslik, A. Hrycek, P. Klucinski** – Vasculopathy and vasculitis in systemic lupus erythematosus. *Pol Arch Med Wewn* 2008. 118(1-2):57-63
6. **N. Pipitone, C. Salvarani** – The role of infectious agents in the pathogenesis of vasculitis. *Best Pract Res Clin Rheumatol* 2008. 22(5):897-911
7. **A.F. Eichler, T.T. Batchelor** – Primary central nervous system lymphoma: presentation, diagnosis and staging. *Neurosurg Focus* 2006. 21(5):E15
8. **R. Soffietti et al.** – Guidelines on management of low-grade gliomas: report of an EFNS-EANO* Task Force. *Eur J Neurol* 2010. 17(9):1124-1133
9. **A. Al-Araji, D.P. Kidd** – Neuro-Behcet's disease: epidemiology, clinical characteristics, and management. *Lancet Neurol* 2009. 8(2):192-204
10. **B. Kara, et al.** – DTI Findings of Brainstem Involvement in Langerhans' Cell Histiocytosis. *Clin Neuroradiol* 2010
11. **M. Odaka, et al.** – Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barre syndrome. *Brain* 2003. 126(Pt 10):2279-2290
12. **M. Ito, et al.** – Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. *J Neurol* 2008. 255(5):674-682
13. **G. Taieb, et al.** – A new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids with initial normal magnetic resonance imaging. *Brain* 2011
14. **B.M. Keegan, C. Giannini, S.J. Pittock** – Reply: A new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) with initial normal magnetic resonance imaging. *Brain* 2011. 391
15. **J. List, et al.** – A new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. *Brain*, 2011
16. **T.P. Duprez, C.J. Sindic** – Contrast-enhanced magnetic resonance imaging and perfusion-weighted imaging for monitoring features in severe CLIPPERS. *Brain* 2011
17. **J.A. Guzman-De-Villoria, C. Ferreiro-Arguelles, P. Fernandez-Garcia** – Differential diagnosis of T2 hyperintense brainstem lesions: Part 2. Diffuse lesions. *Semin Ultrasound CT MR* 2010. 31(3):260-274