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Unusual CLIPPERS presentation and role of MRI examination in the proper diagnostic assessment: A case report

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ABSTRACT

Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids syndrome (CLIPPERS) is a newly described, underestimated CNS inflammatory disorder involving predominantly the midbrain and the cerebellum. CLIPPERS pathogenesis is largely unknown, and its clinical manifestations are polymorphic and sometimes confounding. Recently clinical, radiological and pathological diagnostic criteria have been proposed to discriminate CLIPPERS from potential mimickers, but the diagnosis still remains challenging. Here we present the case of a patient with radiological findings consistent with CLIPPERS but with atypical clinical presentation, highlighting the importance of a proper diagnostic assessment.

1. Introduction

Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids syndrome (CLIPPERS) is a rare and recently described Central Nervous System (CNS) sub-acute inflammatory disorder involving predominantly the midbrain and the posterior cranial fossa. Generally characterized by mild clinical symptoms related to brainstem involvement, on Magnetic Resonance Imaging (MRI) it is demonstrated by confluent areas of T2w hyperintensity not significantly exceeding multiple punctate gadolinium-enhancing foci, with exquisite response to immunosuppression with corticosteroid therapy [1].

The pathogenesis of CLIPPERS is largely undetermined, being histologically characterized by a non-specific T-cell lymphocytic perivascular infiltration with co-existent white matter, grey matter and meningeal inflammation [2]. The most accepted hypothesis is that it may represent a CNS lymphocytic reactive response triggered by mechanisms of molecular mimicry, imbalanced immune response or immune reconstitution, with tendency to relapse and possible progression to lymphocytic proliferative disease [3].

With no clear gender and age predilection, CLIPPERS exact prevalence in still unknown [4]; it is likely that the disorder is underestimated and misdiagnosed due to the variable clinical presentation and to the wide spectrum of possible mimickers [5].

Here we present a case of challenging ex juvantibus CLIPPERS diagnosis in a poorly symptomatic patient, with atypical manifestations and no evidence of previous triggering event that could explain the clinical presentation.

2. Case report

A 36-years old man was admitted to the hospital referring a 3-months history of cervical pain, non responsive to non-steroidal anti-inflammatory drugs. He also referred sporadic episodes of confusion and vomiting without fever within the last month. His previous medical history was unremarkable, excepted for a surgical procedure for traumatic radial fracture when he was 12-years old. On neurological examination the patient was conscious and oriented, with normal eyes motion and pupillary reflexes, but positive bilateral gaze-evoked horizontal nystagmus; fundoscopy was normal. Signs and symptoms of meningeal irritation of peripheral nerves involvement were absent, and the remaining physical examination was unrevealing.

Abbreviations: CLIPPERS, Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids; CNS, Central Nervous System; MRI, Magnetic Resonance Imaging; CT, Computed Tomography; CSF, Cerebrospinal fluid; PCGE, punctate and curvilinear gadolinium enhancing lesions

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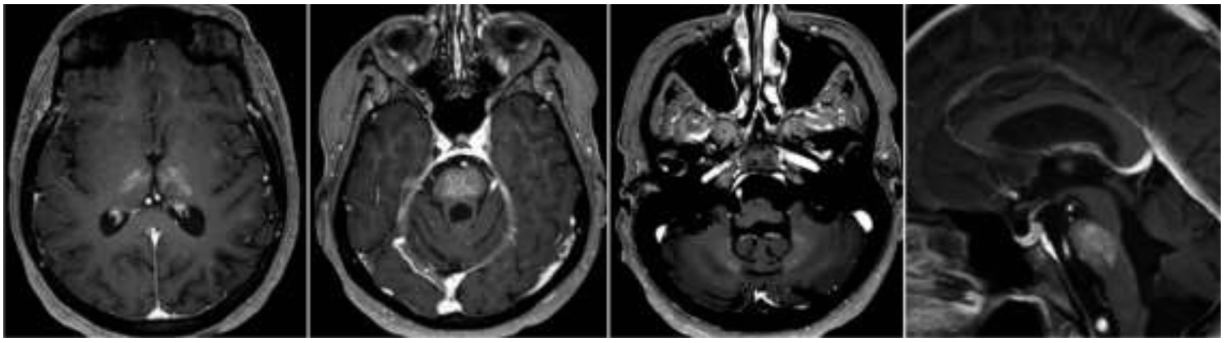

Fig. 1. Post-gadolinium axial and sagittal T1w images at different representative levels, performed at diagnosis.
MRI examination showed punctate symmetrical contrast-enhancement within basal ganglia and pons, extending to adjacent midbrain and middle cerebellar peduncles, as well as to the medial aspects of cerebellar hemispheres.

During hospitalization he experienced severe headache, more intense in the occipital region, not associated with nausea, photo- or phono-phobia. Therefore he underwent Computed Tomography (CT) scan, showing swelling of the pons, with homogeneous and diffuse hypodensity; due to these abnormal findings, brain MRI was also performed. Axial TSE T2w and FLAIR sequenced showed diffuse patchy hyperintensity of the pons and, to a lesser extent, of middle cerebellar pedicles, cerebellar hemispheres and basal ganglia. Contrast–enhanced SE T1w revealed several punctate foci of enhancement with perivascular pattern, almost symmetrical, involving the pons and extending to adjacent midbrain and medial aspects of middle cerebellar peduncles; some sporadic foci of enhancement were also detectable within the cerebellar hemispheres and basal ganglia (Fig. 1). There was no evidence of leptomeningeal enhancement, and the spinal cord was normal. Axial DWI and relative ADC map showed no focal area of restricted signal, and no susceptibility change was visible on GRE T2w.

Blood cell count and biochemical parameters were within normal range, and serum analysis for paraneoplastic and autoimmune antibodies was negative. Serum analysis was also negative for human immunodeficiency virus type 1 and 2, Venereal Disease Research Laboratory test, rapid plasma regain and fluorescent treponemal antibody absorption.

Cerebrospinal fluid (CSF) obtained by lumbar puncture was crystal clear and colourless at visual inspection. Chemical examination showed moderate protein concentrations increase (97 mg/dL; normal range: 12–60 mg/dL), with immunoglobulin G elevation (30.1 mg/dL; normal < 5.9 mg/dL) but no evidence of oligoclonal bands; glucose, lactate, and cell count were normal. CSF antigen and antibody testing for infectious agents were also negative, as well as flow cytometry for the search of monoclonal lymphoid population.

The suspicion of CLIPPERS was then raised. The patient underwent treatment with high-dose intravenous Methylprednisolone 1 g/day over 5 days, followed by a maintenance dose of Prednisone 10 mg/day. A significant clinical improvement occurred after few days of therapy. The control brain MRI performed after 1week from the beginning of the treatment revealed a reduction in number and size of the T2w hyperintense areas of the midbrain with a simultaneous decrease of the punctate foci of contrast enhancement on T1w images, more evident in the cerebellar hemispheres (Fig. 2). This parallel clinical and radiological evolution, depending on the effective treatment with corticosteroids, confirmed ex juvantibus the diagnosis of CLIPPERS. Unfortunately, when rebuilding patient's previous medical history, no trigger event that could potentially explain CLIPPERS pathogenesis was discovered. The follow-up MRI examination performed 6 months later showed the regression of midbrain and cerebellar lesions, with complete restitutio ad integrum.

3. Discussion

CLIPPERS syndrome is histologically characterized by a marked T-cell predominant lymphocytic perivascular inflammation with simultaneous involvement of white matter, grey matter, and meninges. Inflammatory infiltrate is mainly represented by CD4+ T-lymphocytes, with scattered macrophages, CD20+ B-lymphocytes and mature-appearing plasma cells, as well as occasional evidence of transmural lymphocytes and inflammatory vessel occlusion [2,4].

CLIPPERS is actually defined by the combination of clinical, radiological and pathological criteria [2]. Neuropathological findings are essential for the diagnosis of *definite CLIPPERS*, but biopsy should be limited to those cases where an alternative pathology is strongly suspected and possible differential diagnosis must be excluded [5–9]. Indeed, recently proposed diagnostic criteria introduced the definition of *probable CLIPPERS*, based on the simultaneous presence of clinical and radiological evidences when neuropathology is not available, as in our case.

CLIPPERS diagnostic suspicion largely relies on the principle of "no better explanation" for the clinical presentation. Most common symptoms are related to brainstem, cranial nerve and cerebellar dysfunction such as ataxia, dysarthria, diplopia or facial dysesthesia, with or without cognitive dysfunction and myelopathy [4]. Headache is not generally reported among typical symptoms, but it may presumably represent another possible and more atypical onset [4,10,11]. As in our report, this clinical presentation is non-specific and confounding, being not strictly referable to brainstem or cerebellar involvement.

In such a situation, neuroimaging represents the most important tool for excluding alternative pathologies and confirming the suspected CLIPPERS diagnosis. Radiological features highly suggestive for CLIPPERS include brainstem punctate and curvilinear gadolinium enhancing lesions (PCGEs) not exceeding T2w hyperintensity, with no significant tissue swelling or mass effect. Lesions are generally localized in pons and middle cerebellar pedicles, with a variable extension to cerebellar hemispheres, brain and spinal cord [8,12,13]. Although evocative of CLIPPERS, PCGEs can also be identified in other infiltrative and inflammatory disorders, making the differential diagnosis challenging [8]. Therefore, the fulfillment of the radiological criteria proposed by Tobin et al. (homogeneous Gadolinium enhancing nodules < 3 mm in the pons and cerebellum; no mass effect or ring enhancement; homogeneous T2w hyperintensity not significantly exceeding the size of Gadolinium enhancement) is crucial for the correct assessment.

The final diagnosis ultimately relies on the marked clinical and radiological improvement with corticosteroid treatment. Indeed, as in our case, disappearance of referred symptoms and regression of abnormal gadolinium enhancement at MRI examination after high-dose intravenous corticosteroids therapy represent the key criterion to confirm ex juvantibus the diagnosis of CLIPPERS.

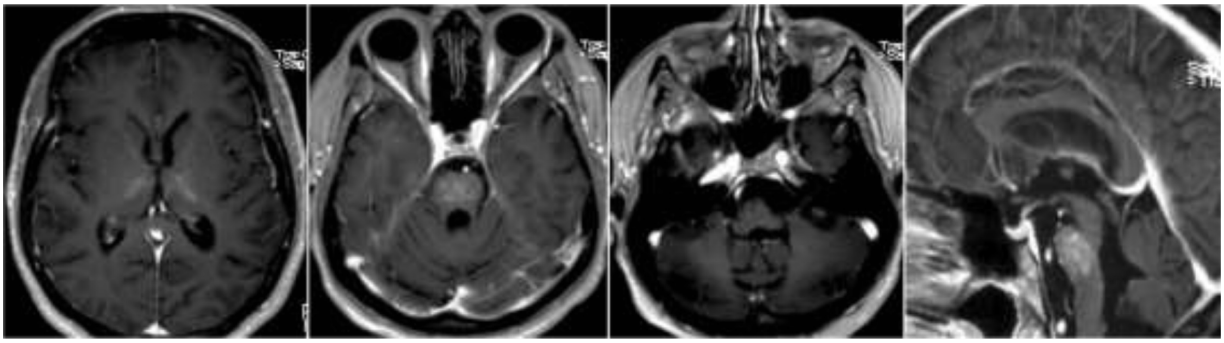

Fig. 2. Post-gadolinium axial and sagittal T1w images at the same levels 1 week after the beginning of corticosteroid therapy.
MRI examination revealed a reduction in number and size of contrast-enhancement foci within basal ganglia and midbrain, with a complete regression of enhancing nodules in cerebellar hemispheres and pedicles.

CLIPPERS was initially considered an immune-mediated CNS disorder, associated to specific trigger events responsible for transient or permanent immunologic derangement, including vaccination, HBV infection, or long-term natalizumab treatment [3,5,14]. Nevertheless, the search for possible causative events of CLIPPERS is often difficult and inconclusive. In our case all the clinical and anamnestic data were unremarkable, with no history of recent vaccination, infection, immunological disorder, or immune therapies. In this light, since CLIPPERS has also been described as early stage or sentinel lesion of primary CNS lymphoma [6,8,15], a long-term MRI follow-up is mandatory to role out the potential malignant evolution. Six months contrast-enhanced MRI follow-up of our patient excluded such a case and showed the complete regression of midbrain and cerebellar lesions.

In conclusion, despite the efforts to clarify its pathogenesis, CLIPPERS syndrome remains a controversial nosological entity. Recently proposed diagnostic criteria [2] are useful to implement diagnostic confidence, but they are not yet completely reliable in absence of neuropathological confirmation due to the polymorphic and sometimes confounding CLIPPERS presentation. Therefore typical neuroimaging features along with prompt response to therapy still represent key features to confirm ex juvantibus the diagnosis of CLIPPERS; biopsy should be limited to those cases where alternative diagnoses are strongly suspected.

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Conflict of interest

The Authors declare that there is no conflict of interests regarding the publication of this paper.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Authors contribution

All authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data according to ICMJE recommendations.

All those who have made substantive contributions to the article have been named as authors

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