CASE STUDY

A RARE BRAINSTEM INFLAMMATORY SYNDROME, CLIPPERS, MYTH OR FACT. CASE REPORT WITH CRITICAL REVIEW

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ABSTRACT
A very rare inflammatory disease of CNS, CLIPPERS syndrome, was recently described and only a few sporadic cases are reported in the medical literature. Its etiology and pathogenesis are unknown, that together with the polymorphic and sometimes confounding neurological manifestations, and radiological findings represent a real diagnostic and therapeutic challenge for clinicians. Aim: To highlight the importance of clear and specific diagnostic assessment. Here we present the case of a 40-year-old male with a subacute lymphocytic midbrain inflammation accompanied by vasculitis. We discuss the symptoms, imaging and treatment of this lesion.

KEY WORDS: brainstem, pons, encephalitis, steroids

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INTRODUCTION

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare CNS inflammatory disorder affecting prominently the brainstem and particularly the pons and adjacent areas such as the cerebellum [1]. It was shown that two main peculiar properties are essential to characterize the case as CLIPPERS; one of them is the classic MRI findings of post-gadolinium enhancing punctate and curvilinear lesions "peppering" in these areas with appropriate clinical manifestation. The second requirement for a correct diagnosis is a dramatic clinical and radiological response to glucocorticosteroid (GCS) based immunosuppression. So, the diagnosis of CLIPPERS is based on clinical presentation, radiographic findings, response to steroids, and exclusion of other diagnoses with imaging, serum and CSF laboratory testing [2].

Although the underlying pathogenesis of this condition is poorly understood and the neuropathological findings are far from specific, there is reason to believe that this pathology has characteristic signs of an immune-mediated inflammatory disorder with a pronounced vascular and perivascular tropism predominantly located in the pons and the peripontine region [3]. However, the ultra-high-field MRI at 7.0T revealed perivascular inflammation not only in the brainstem and cerebellum but also in brain areas with normal imaging on 3.0T MRI [4]. The immune-based nature of CLIPPERS has recently been confirmed. It was determined, CD45+ lymphocytes with a predominance of CD3+ T cells and CD4+ T cells were accumulated in vessel walls and perivascular area of brainstem and cerebellum of patients with CLIPPERS. CD4+ T cells also infiltrated the brainstem parenchyma. The presence of CD8+ T cells was less pronounced and only a few CD20+ B cells were observed [4]. The omics-based approach showed importance of cell adhesion molecules (VCAM-1, ICAM-1) and interleukins (IFN-γ, TNF-β, IL-1, IL-6, IL-10) upregulation, and IgG deposition in the pathogenesis of CLIPPERS but the central role, certainly, belongs to complement activation [4]. This allows them to be considered potential targets for the treatment of CLIPPERS. The monoclonal antibodies are very promising in this regard and first positive results already published [5]. It's tocilizumab – IL-6 receptor-blocker provides the long-standing relapse-free time period even in the patients with various relapses and nonresponse to multiple agents. Immunosuppressive effects of tocilizumab are thought to be a result of the induction and expansion of B-regulatory cells as well as the differentiation of T cells into effector or regulatory T cells with a significant increase of regulatory T cells [5]. In addition, upregulated VCAM-1, ICAM-1, IL-8, and eotaxin in the CSF may be potential biomarkers in CLIPPERS.

In this case report, we demonstrate that early recognition of this syndrome and a directed diagnostic approach make treatment more effective, patient outcomes earlier, and limit or avoid unwanted complications.

CASE STUDY

A 40-year-old male admitted to the Center of Infectious Disorders of the Nervous System, Kyiv, Ukraine (CIDNS)

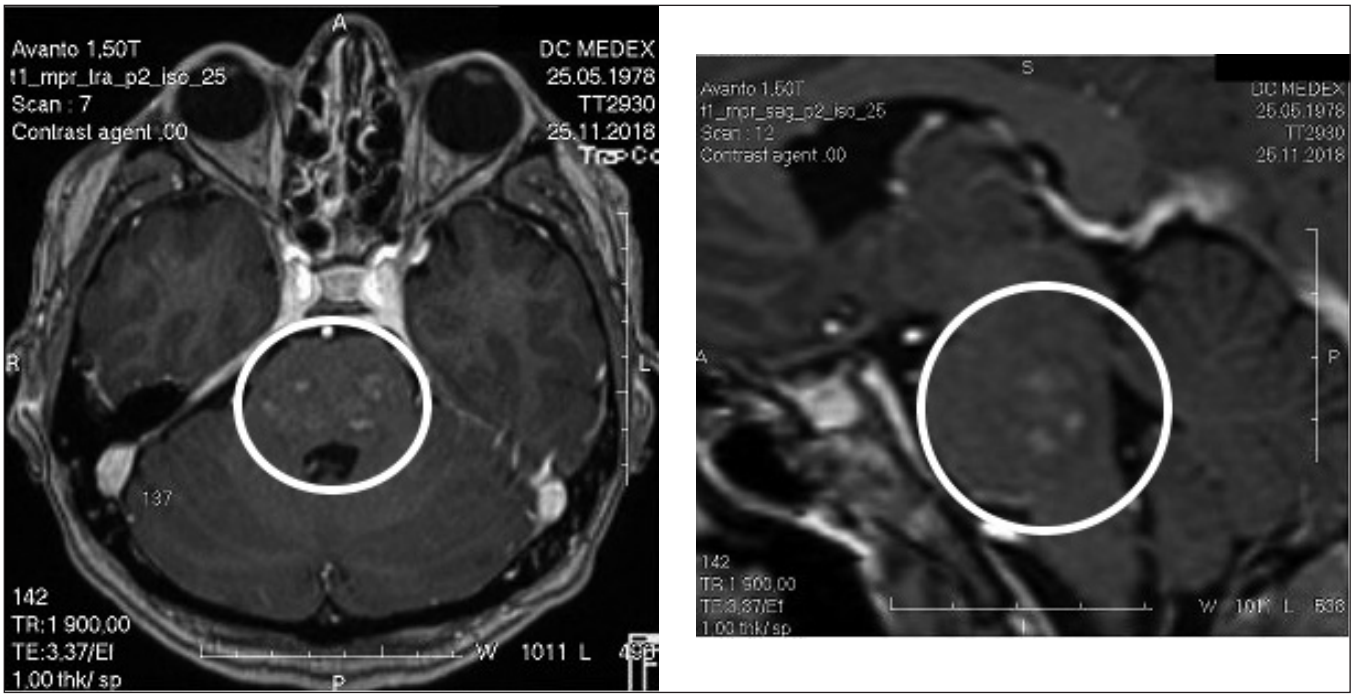

Fig. 1. MR images at the post-gadolinium scans, heterogeneous accumulation of contrast in the structure of the indicated region is preserved.

with complaints of sustained dizziness, vertigo, unsteady gait, blurred vision, weakness, fatigue, and decreased performance for more than a month. He has no relevant medical or family history. General clinical examination was normal. Clinical neurologic examination showed diplopia when looking to the left, left-sided facial hypoesthesia, slight deviation of the tongue to the left, light tremor of the hands at complicated Bare-probe. Nery, Stryumpel, Sharapov, and Chaddok symptoms were positive on one or both sides. Meningeal symptoms were not detected. He performed the coordination tests with intent, staggering in the Romberg pose.

A lumbar puncture was performed just on admission and CSF analysis revealed lymphocytic pleocytosis of 16 cell/μl (lymphocytes) with normal protein and glucose. Viral serology for HSV1/2, CMV, EBV, VZV, mumps, adenovirus, and enterovirus was negative. CSF PCR was reported to be negative for DNA of herpesviruses, *M.tuberculosis*, and *Tox. Gondii*. The oligoclonal band also was not revealed.

MR imaging showed a site of the small infratentorial lesions of an inflammatory nature in the pons with spreading to the upper and lower cerebellar peduncles without clear contours, a region of an amplified at T2 W1 and weakened at T1 W1 signal has a total size of 22x47x28 mm, at the post-gadolinium scans, heterogeneous accumulation of contrast in the structure of the indicated region is preserved (Figure 1 and Figure 2).

The patient did not have a brainstem biopsy for neuropathological diagnosis but met the clinical and MRI criteria of CLIPPERS as proposed by Tobin et al. [6], and an extensive workup did not yield an alternative diagnosis. Oral steroid treatment was started with 12 mg of methylprednisolone per day i/v, tapered to 4 mg of methylprednisolone per day during a month, and accompanied with a variety of steroid-sparing agents. We observed marked improvement of the clinical symptoms and partial resolution of MRI lesions after the use of methylprednisolone.

DISCUSSION

CLIPPERS Syndrome is chronic inflammation with a disorder of the pons, MR imaging of the contrast enhancement of the perivascular spaces in the pons, which responsive to steroids. The disease is extremely rare, its etiology and pathogenesis remain unknown. Although a full set of diagnostic criteria has not yet been determined MRI finding showing punctate enhancement in a "pepper-like appearance" centred on the pons is regarded as the hallmark of CLIPPERS [1, 6]. However, new data show involvement in the inflammatory process of remote areas of the brain and spinal cord, which reduces the diagnostic value of neuroimaging findings [4]. Besides, such clinical and neuroimaging findings can occur at other pathologies and therefore cannot be considered quite specific [7, 8]. The diagnostic value of the second important criterion, response to steroids, seems even more controversial. Indeed, almost all diseases with a pronounced inflammatory component respond to immunosuppressive drugs, including steroids. Not surprising, corticosteroid therapy was typically associated with the disappearance of neurologic symptoms and regression of post gadolinium contrast enhancement [6]. So, successful steroid therapy is the crucial criterion to confirm ex juvantibus the diagnosis of CLIPPERS. However, the clinical effect of steroids is usually temporary and rare radical. Disease progression is accompanied by a reduction in remissions and a weakening effect. The final component of the differential diagnostic scheme, the absence of other alternative causes,

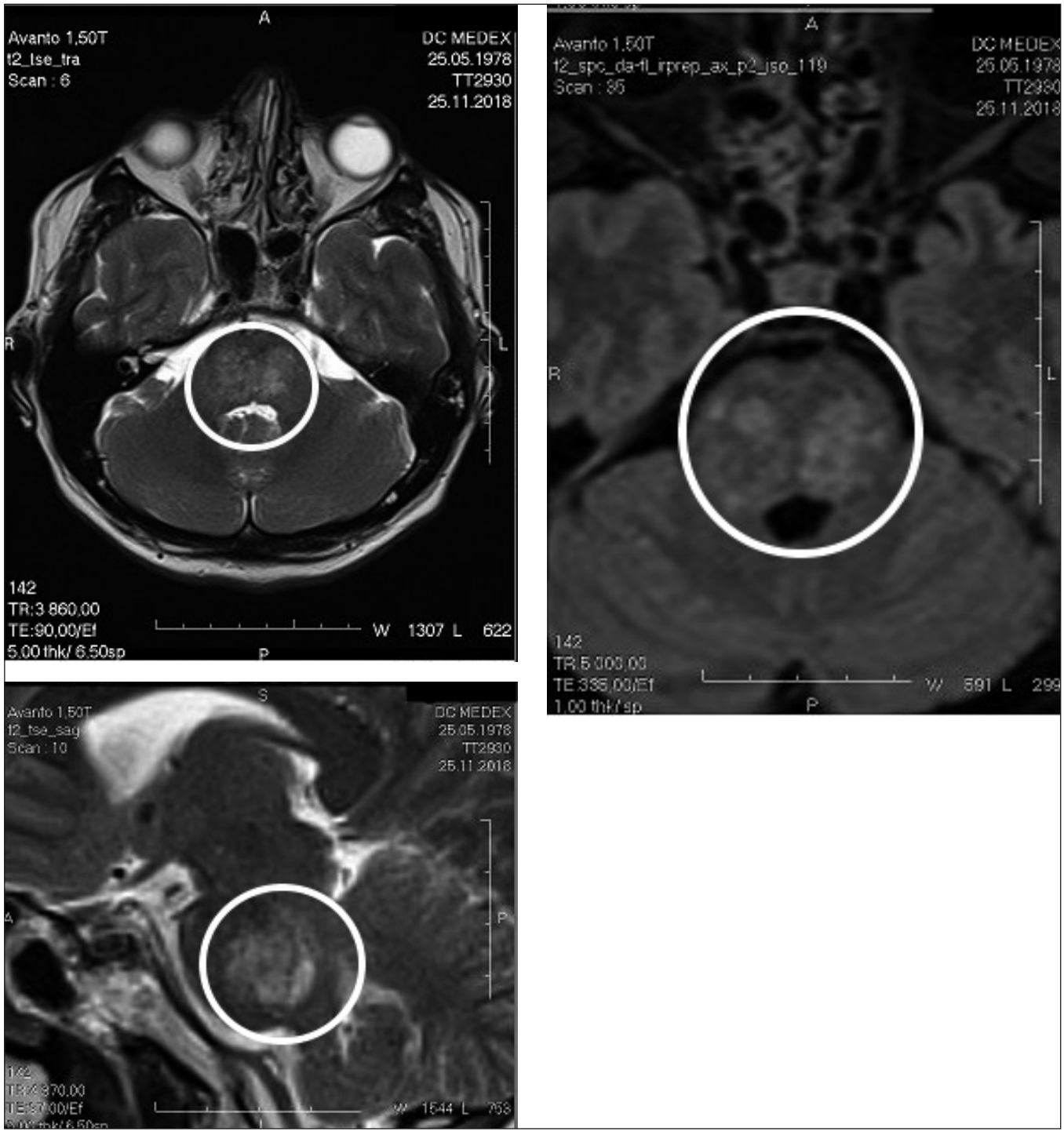

Fig. 2. MR images of an inflammatory nature disorders in the pons with spreading to the upper and lower cerebellar peduncles without clear contours, a region of an amplified at T2 W1 signal has a total size of 22x47x28 mm.

seems to be the most important. Indeed, some patients initially diagnosed with CLIPPERS syndrome because of the characteristic clinical and radiological symptoms later turned out to be an atypical presentation of malignant lymphoma and other inflammatory and no inflammatory disorders [2, 9]. So, the exclusion of other possible causes of the identified abnormalities is a necessary condition for a correct diagnosis.

CONCLUSIONS

CLIPPERS syndrome appears to be a mysterious and uncommon variant of encephalitis involving inflammation of the brain parenchyma and vasculitis, which represent a real diagnostic challenge for health practitioners. Despite the efforts to clarify its pathogenesis, CLIPPERS syndrome remains a controversial nosological entity. It is thus necessary to evoke the diagnosis in front of any encephalitis etiologic

reason of which does not prove, particularly if recurrent and in elderly. Early diagnosis and adequate management can improve the prognosis of this disease. However, the low specificity and ambiguity of the proposed diagnostic symptoms do not allow to confidently differentiate CLIPPERS, which makes the search for new diagnostic tools and symptoms highly relevant.

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Conflict of interest:

The Authors declare no conflict of interest.

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