

Case report



CLIPPERS SYNDROME – MRI FEATURES AND DIAGNOSTIC IMAGING FOLLOW-UP IN A PATIENT – CASE DISCUSSION AND REVIEW OF THE LITERATURE

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ABSTRACT

Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) syndrome is a rare neurological disorder with uncertain etiology, pathogenesis and clinical course. Pittock et al. in 2010 first described this chronic inflammatory neurologic condition, which preferably affects the brainstem. There is an infiltration with inflammatory cells of the affected regions and typical dotted and curvilinear contrast-enhancement zones on magnetic resonance imaging (MRI), including leptomeninges. I present one case of a 41-year-old male with gradual onset of suspected infectious disease and neurological worsening with typical MRI features, with a biopsy confirmed diagnosis and follow-up for 15 months. The MRI findings and the evolution of the disease can narrow the differential-diagnostic spectrum in such a clinical case.

Keywords: CLIPPERS, brainstem, MRI,

INTRODUCTION:

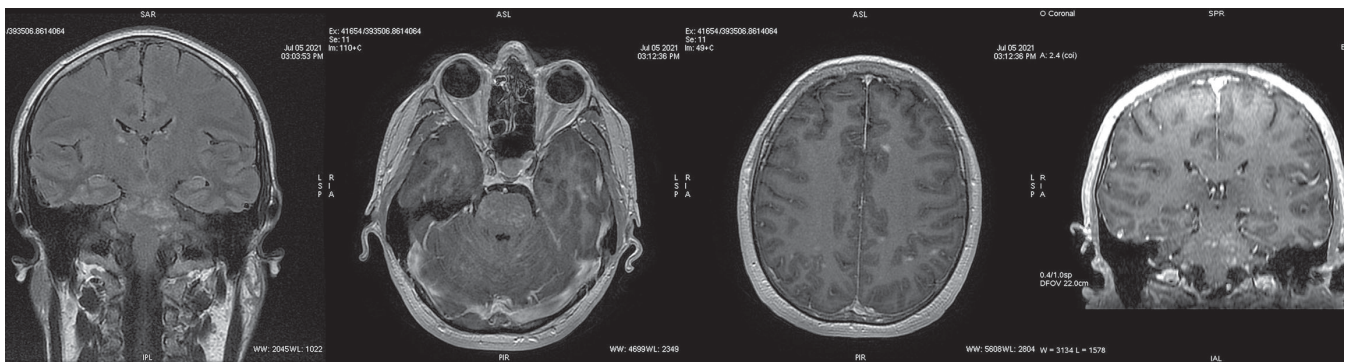
CLIPPERS syndrome is a kind of encephalomyelitis that affects mainly the brainstem but can involve other regions like the spinal cord, cerebral white matter, corpus callosum, cerebellum, thalami, basal ganglia [1]. Clinical presentation is varied and includes diplopia, ataxia, dysarthria, altered sensation and spasticity, including spas-

tic paraparesis, with intact cognition and without fever or meningism [1, 2]. The course of the disease is relapsing, remitting with progression during the relapses [1]. The neuropathology reveals predominantly T-cell lymphocytic infiltrates in the perivascular white matter [3]. Neuroimaging shows multiple punctiform or curvilinear gadolinium-enhancing lesions in the pons, cerebellum, midbrain, spinal cord, basal ganglia, and white matter [4, 5]. It is an autoimmune disorder, in most cases with a good response to cortico-steroid therapy and sometimes long-term immunosuppression must be included [1, 3, 6].

CASE DESCRIPTION:

Our patient is a 41-year-old male who arrived in Bulgaria after a sea voyage to China. On 24. 06. 2021, bilateral pneumonia was established in outpatient settings, and he started antibiotic treatment. On 05. 07. 2021, the patient came to our hospital with a headache, confused and disoriented, with numbness in the left arm. The chest X-ray, Chest and head CT, and abdominal ultrasound were normal. COVID-19 fast test and later PCR were negative. The MRI of the head on 05. 07. 2021 showed multiple, sometimes confluent pathological subcortical contrast-enhancing lesions supra- and infratentorial, leptomeningeal, in the pons and in the basal ganglia, possibly as an expression of perivascular spread, measuring from 2 mm to 20 mm (Fig. 1).

Fig. 1. Postcontrast COR T2 FLAIR+C, AX 3DT1+C at the level of the pons and centrum semiovale, COR 3DT1+C at the level of the pons showing multiple contrast-enhancing lesions in the pons, cerebellum, perivascular white matter.

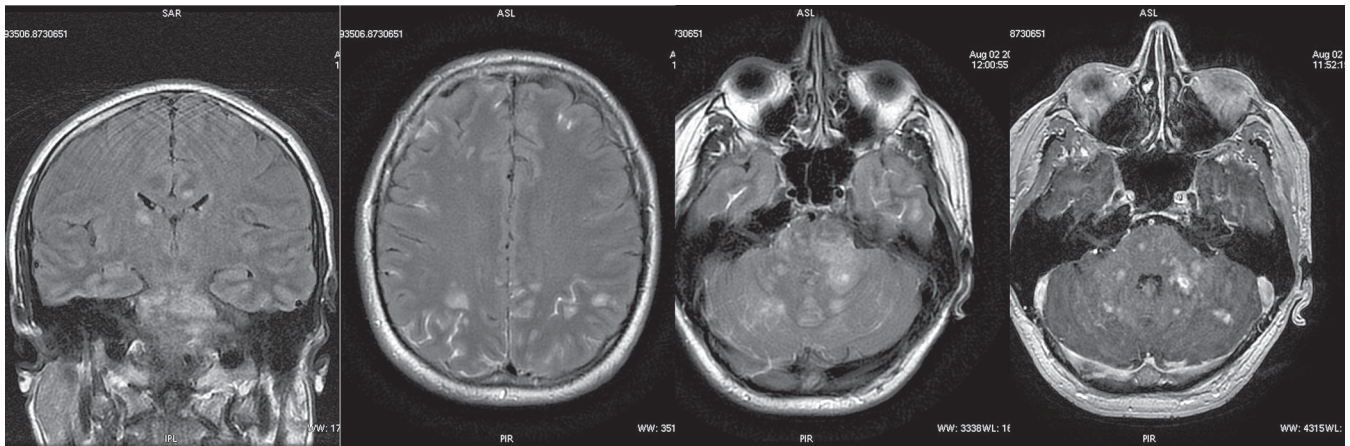


Lesions were almost isointense on T1, hyperintense on T2, with no diffusion restriction, no hemosiderin deposits, with homogenous enhancement, including leptomeningeal, and our differential diagnosis included encephalitis, fungal infection, tuberculosis, CNS lymphoma, metastases, and sarcoidosis. After stabilization of the condition, the patient was discharged with a diagnosis of viral encephalitis.

On 02. 08. 2021, he was hospitalized again febrile

with a temperature of 38.7°C. The chest CT revealed inflammatory changes in the lungs, like ground glass opacities and some zones of consolidation. PET-CT confirmed the inflammatory changes in the lungs and excluded other pathology. Two MRI examinations on 02. 08. 2021 and on 17. 08. 2021 showed progression in size and the distribution of the known contrast-enhancing brain lesions as well as the leptomeningeal enhancement, with some lesions also having perifocal edema (Fig. 2).

Fig. 2. COR T2 FLAIR, postcontrast AX T2 FLAIR+C at the level of centrum semiovale and pons, and postcontrast AX 3D T1+C showing the progression of the lesions and the leptomeningeal enhancement.



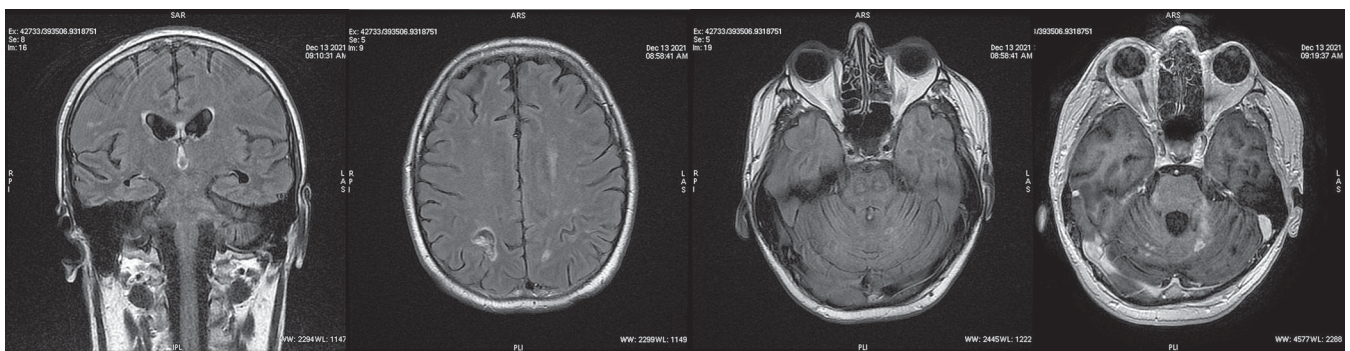
Flowcytometry showed T-cell lymphopenia and activation of T lymphocytes (CD 38 and HLA-DR) without any pathologic clonal population. The CSF examinations showed the presence of mature and activated lymphocytes without tumor cells and were negative for CMV, HSV-1, VZV, Syphilis, HIV. The immunologic examinations for antibodies in autoimmune encephalitis (anti-NMDARH, anti AMPA1/2R, anti DPPX, anti CAPR2) were negative. The patient is discharged persistently afebrile with quadriplegia and mild psycho-organic syndrome. In the differential diagnosis remained, viral encephalitis and sarcoidosis.

On 09. 09. 2021, the patient was hospitalized for the third time without any significant difference in the clinical, laboratory and diagnostic imaging findings, including

the fourth MRI examination of the brain.

In November 2021, the patient underwent a brain biopsy in a Turkish hospital, part of Johns Hopkins Medicine International, with a result: CLIPPERS syndrome. Treatment with steroids started, and the patient had an ambulatory follow-up MR examination in our institution, which showed reverse development of the MRI changes - reduction of the number and the volume of the known contrast-enhancing lesions, lack of edema, changes in the signal of the lesions - more pronounced T2 hypersignal and T1 hyposignal, and reduction of the contrast-enhancement, even with non-contrasting lesions (Fig. 3). Also, ventriculomegaly, and slight cortical atrophy changes in frontal-parietal and medio-temporal (including hippocampi) regions were reported.

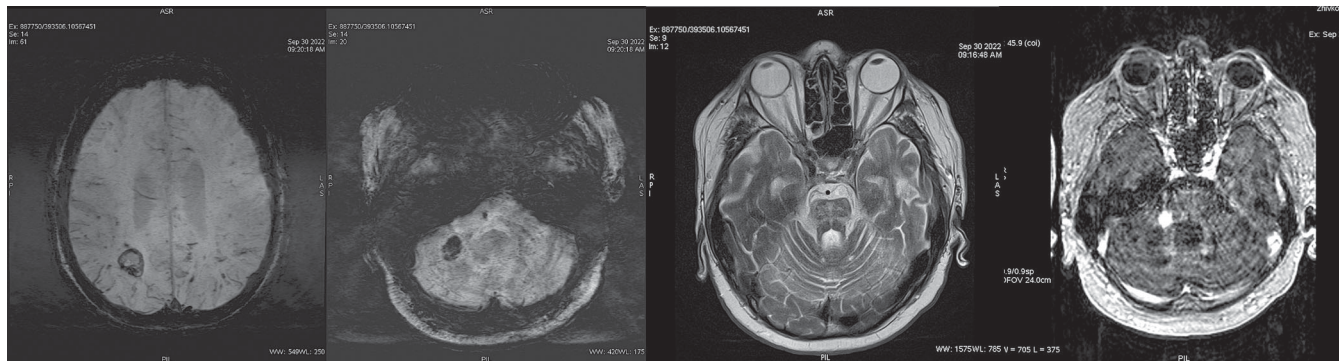
Fig. 3. COR T2 FLAIR, AX T2 FLAIR at the level of centrum semiovale and the pons, postcontrast AX 3DT1+C at the level of the pons showing reduction of the number, distribution, and the contrast-enhancement of the known brain lesions.



The next 4 follow-ups MRI examinations on 10. 03. 2022, 19. 04. 2022, 04. 07. 2022 and 30. 09. 2022 revealed continuing reduction in the volume and the contrast-enhancement of the lesions. The images from the last MR ex-

amination made on the 3T machine also showed a slight progression of atrophy and ventriculomegaly, as well as small anintense zones on the SWI series, resulting from small hemosiderin deposits (Fig. 4).

Fig. 4. AX SWI sequence at the level of centrum semiovale and the pons revealed multiple anintense zones of hemosiderin deposits, AX T2 and AX 3DT1+C postcontrast at pontine level showed growing atrophic changes and gliosis, with a single contrast-enhancing lesion.



The patient conducted active rehabilitation at home, and his relatives reported clinical improvement during this period.

DISCUSSION:

CLIPPERS syndrome is a rare disorder with uncertain etiology and unknown mechanism, which diagnosis relies on the clinical, MRI, laboratory, and pathological findings and response to corticosteroid treatment [1, 3, 8].

This CNS disorder dates from 2010, and till now, about 56 cases have been reported [1, 9]. Typically, middle aged patients are affected, with slight male predominance [1, 8], as in our case. The clinical manifestation consists of headache, diplopia, dysarthria, ataxia, altered sensation and spasticity, which we also observe in our patient. The MRI findings are punctiform or nodular lesions in the pons, cerebellum, cerebral white matter with homogenous contrast enhancement, hyperintense on T2, with volume not significantly exceeding the T1 enhancement, with decreased perfusion, without diffusion restriction [9, 10]. In our case, lesions were with the same MRI signs and bilateral distribution, concentrated in the pons and cerebellar peduncles, but also found in centrum semiovale, some lesions were with slight perifocal edema. The MR angiography was normal, the arterial spin labelling (ASL) perfusion study did not show any significant changes, although with motion artefacts. Bilateral brain involvement is typical, and the corticosteroid treatment affects fast the clinical symptoms and reduces the volume and contrast enhancement of the lesions, which we also saw in our patient. These are important features of CLIPPERS syndrome. Otherwise, many other diseases could mimic this disorder, like: Hodgkin, B cell and T cell CNS lymphoma,

Erdheim-Chester disease, multiple sclerosis, neuromyelitis optica, neurosarcoidosis, Behcet's disease, Bickerstaff's encephalitis, primary brain angiitis, chronic hepatitis B infection, CNS lymphomatoid granulomatosis [7, 10, 11, 12].

Brain biopsy result shows lymphocytic infiltration with perivascular and parenchymal distribution, with both white and grey matter involvement [13]. T cells predominate with a differently expressed macrophage component, most of them CD3 positive, also CD4 positive has been reported [13, 14].

CLIPPERS is not a benign condition, there are reports for possible conversion to lymphoma [14, 15], neurological decline with brainstem and cerebellar atrophy [16].

In our case, the differential diagnosis remained encephalomyelitis, neurosarcoidosis, but the absence of marked CSF pleocytosis ($>100/\mu\text{l}$), negative work-up for infection, lack of abnormal lymphocyte clonal population, negative PET-CT, characteristic MRI findings, brain biopsy result and rapid treatment response after corticosteroids therapy tipped the scales in favor of this diagnosis – CLIPPERS syndrome.

CONCLUSION:

CLIPPERS syndrome is a rare neurological disorder and is a diagnosis of exclusion. There are no confirmed criteria for this syndrome, but putting together pathological, clinical, and radiological features along with follow-up and treatment response could recognize this condition and contribute to the elucidation of its etiology, pathogenesis, treatment, and prognosis.

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