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Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) – a case report

Przewlekłe limfocytarne zapalenie mózgu odpowiadające na leczenie sterydami (CLIPPERS) – opis przypadku

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Abstract

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a newly described inflammatory disease of the central nervous system. The diagnosis is based on the clinical, radiological and neuropathological findings. Prominent response to steroids is also a characteristic diagnostic feature of the disorder. We present a case of a patient with probable CLIPPERS disease as well as discuss treatment and differential diagnosis. The patient received chronic immunosuppressive treatment with the use of steroids and steroid-sparing agent (methotrexate), which led to clinical and radiological improvement. There are no treatment guidelines due to the limited number of such cases. The knowledge of this disorder is important for neurologists and radiologists.

Keywords: brainstem encephalitis, CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, encephalitis, vasculitis

Streszczenie

Przewlekłe limfocytarne zapalenie mózgu odpowiadające na leczenie sterydami (CLIPPERS) to nowa jednostka chorobowa ośrodkowego układu nerwowego na podłożu zapalnym. Rozpoznanie ustalane jest na podstawie obrazu klinicznego, radiologicznego i neuropatologicznego. Charakterystyczny oraz diagnostyczny objaw stanowi wydatna odpowiedź na leczenie sterydami. Prezentujemy opis przypadku pacjenta z prawdopodobnym zespołem CLIPPERS oraz informacjami dotyczącymi diagnostyki różnicowej i leczenia. U pacjenta wdrożone zostało przewlekłe leczenie immunosupresyjne w postaci sterydów oraz leku „oszczędzającego sterydy" (metotreksat), co skutkowało kliniczną i radiologiczną poprawą. Aktualnie brakuje wytycznych dotyczących leczenia z uwagi na ograniczoną liczbę przypadków tej jednostki chorobowej. Wiedza dotycząca omawianego schorzenia jest ważna dla neurologów oraz radiologów.

Słowa kluczowe: zapalenia pnia mózgu, CLIPPERS, przewlekłe limfocytarne zapalenie mózgu odpowiadające na leczenie sterydami, zapalenie mózgu, zapalenie naczyń

INTRODUCTION

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) was described for the first time by Pittock et al. in 2010. This new disease is a chronic, inflammatory disorder of the central nervous system (CNS). More than 50 patients with such diagnosis have been described so far. The histopathological presentation includes white matter perivascular lymphocytic and histiocytic infiltration with or without parenchymal extension. Perivascular CD3+ and CD4+ T cell lymphocytic inflammation with a smaller population of CD20+ B lymphocytes is observed (Dudesek et al., 2014; Zalewski and Tobin, 2017). This chronic inflammatory process leads to predominant involvement of brainstem, cerebellum and spinal cord. The onset of symptoms is usually subacute and manifests with characteristic symptoms indicative of the localisation. The most common manifestations include: gait ataxia (91%), diplopia (61%), facial sensory changes (48%), dysarthria (43%), cognitive impairment (39%), and vertigo (36%) (Tobin et al., 2017). Other, less common, symptoms may also be observed: dysgeusia, dysphagia, long tract symptoms, hoarse voice, hiccup, nausea, neurogenic bladder, tremor, abnormal fatigue (Dudesek et al., 2014). Steroid treatment is usually very effective with subsequent addition of steroid-sparing drugs.

Tobin et al. (2017) proposed diagnostic criteria for probable and definite CLIPPERS. Probable diagnosis may be established based on the clinical and radiological findings. Definite diagnosis requires all criteria: clinical, radiological and neuropathological. The probable diagnosis of CLIPPERS requires fulfilling all clinical and radiological criteria (Tab. 1).

We describe a case report of a patient diagnosed with the CLIPPERS syndrome along with the diagnostic procedures performed. We also present the clinical and neuroimaging follow-up.

CASE REPORT

A 42-year-old female Caucasian patient suffered from gait difficulties, imbalance, vertigo, abnormal sensation in the face, hands, feet and buttocks for 3 months. She also reported diplopia, hyperacusis, hyperosmia, decreased appetite, tingling in the tongue, soft palate, cheeks and lips. On examination we detected dysarthria, decreased superficial sensation on the face in the onion-like distribution and the tongue, bilateral cerebellar ataxia with left-sided predominance, and bilaterally increased deep tendon reflexes. Ophthalmological examination of the optic nerve was normal.

Neuropsychological examination detected cognitive disorders: short-term verbal memory and procedural memory deficits, executive dysfunctions, articulation impairment, hand–eye coordination and psychomotor speed disorders. As for memory and the ability to acquire new information, the California Verbal Learning Test (CVLT) demonstrated mild deficiency in learning: low results of direct recollection, flat learning curve with dominant recency effect, many perseveration and intrusion errors in learning process, moderate problems with recognition. Executive dysfunctions were dominant in the patient, especially in recalling information. There were also difficulties with planning, slower pace of intellectual processes and attention disorders.

Brain magnetic resonance imaging (MRI) with gadolinium enhancement showed the presence of punctate foci of enhancement in T1-weighted post-gadolinium scans within the T2-hyperintense area in pons, midbrain, cerebellum, right thalamus, white matter of occipital lobes and a very small foci only of gadolinium enhancement in the white matter of both hemispheres (Fig. 1).

The follow-up examination performed after 6 months showed significant regression of these changes with less gadolinium-enhancing lesions (Fig. 2).

Diagnostic criteria	
Clinical	1. Subacute pontocerebellar dysfunction, with or without other CNS symptoms, such as cognitive dysfunction and myelopathy 2. CNS symptoms responsive to corticosteroid therapy 3. Absence of peripheral nervous system disease 4. Lack of alternative better explanation for clinical presentation
Radiological (magnetic resonance imaging)	1. Homogenous, gadolinium enhancing nodules without ring enhancement or mass effect predominating in the pons and cerebellum, measuring <3 mm in diameter 2. Marked improvement in abnormal gadolinium enhancement with corticosteroid treatment 3. Homogenous T2 signal abnormality where the degree of T2 does not significantly exceed the size of the area of post-gadolinium enhancement 4. Spinal cord lesions with similar T2 and gadolinium enhancing lesions as above
Neuropathological	1. Dense lymphocytic inflammation with perivascular predominance and parenchymal diffuse infiltration; both white and grey matter could be involved 2. T-cells predominating infiltration (CD4 > CD8) with variable macrophage components 3. Absence of myelin loss or focal secondary myelin loss 4. Lack of alternative better explanation for pathological presentation

Tab. 1. Diagnostic criteria for CLIPPERS syndrome (Tobin et al., 2017)

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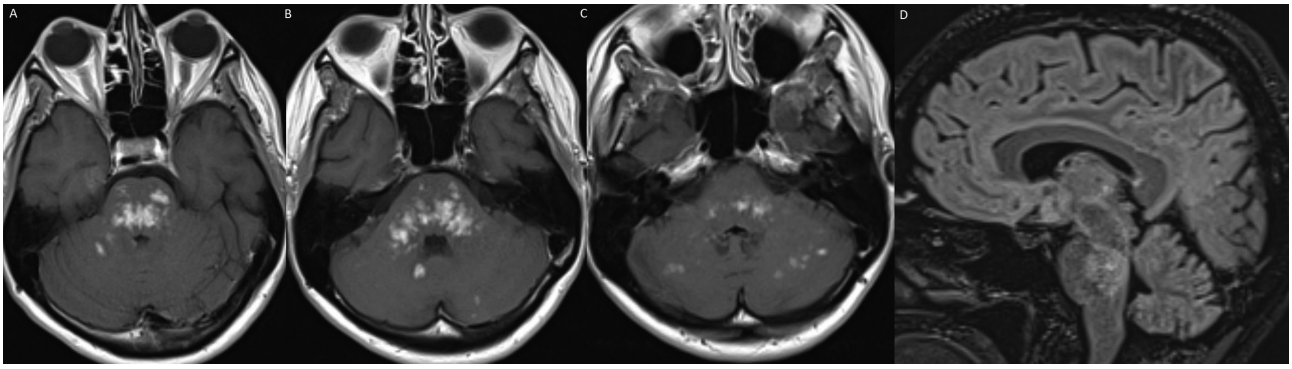

*Fig. 1. The initial brain MRI: T1-weighted post-gadolinium axial scan (***A–C***), T2-weighted sagittal scan (***D***)*

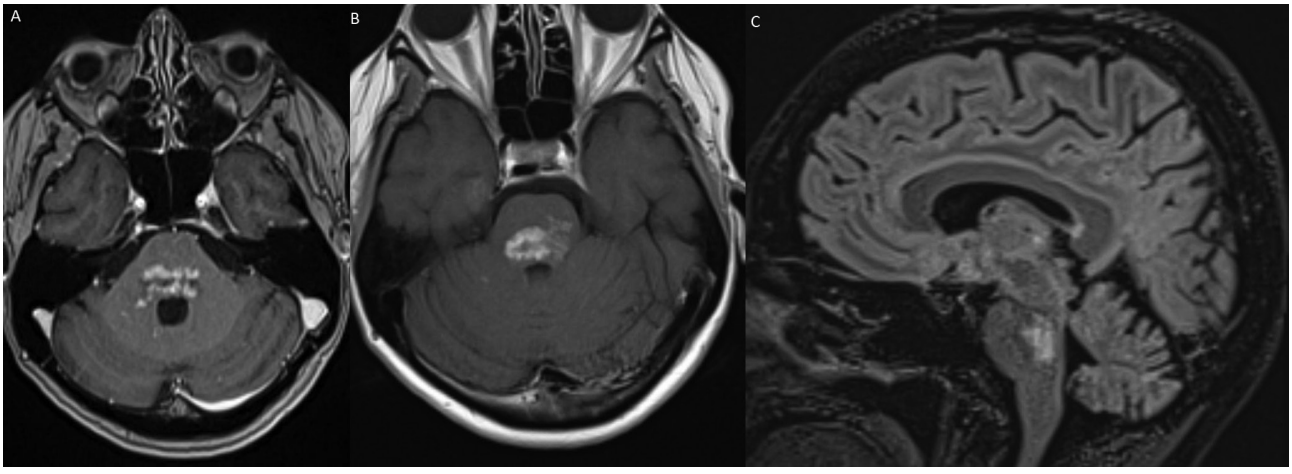

*Fig. 2. The follow-up brain MRI: T1-weighted post-gadolinium axial scan (***A, B***), T2-weighted sagittal scan (***C***)*

Cervical spine MRI did not show any abnormalities within the spinal cord. Chest computed tomography did not reveal any abnormalities within the chest; of note was the enlargement of the left axillary lymph nodes. Due to this finding, the patient underwent haematological assessment and bone marrow biopsy with flow cytometry testing, which showed no abnormalities.

Additional routine and more specific blood tests were performed to exclude rheumatological, haematological, infectious, neoplastic and paraneoplastic causes as well as neuromyelitis optica.

Detailed cerebrospinal fluid (CSF) analyses did not reveal any abnormalities (routine analysis, IgG and IgM borrelia antibodies, oligoclonal bands, IgG index, CMV DNA, EBV DNA, HSV-I DNA, HSV-II DNA, HHV-6 DNA, HHV-7 DNA, B19 parvovirus DNA, parechovirus RNA, enterovirus RNA, adenovirus DNA).

The initial treatment used methylprednisolone at a dose of 1 g for 5 days intravenously with subsequent chronic methylprednisolone 40 mg per day and methotrexate 7.5 mg/week. We observed significant improvement of the symptoms directly after IV steroid therapy, but the cerebellar symptoms did not resolve completely. After 6 months of treatment, the dose of methylprednisolone was reduced to 32 mg per day. Subsequently, the subjective sensation of imbalance increased and periodic diplopia occurred, leading to transitory increase of the steroid dose up to 40 mg despite gradual resolution of lesions in MRI scans. Further observation and clinical improvement allowed to continue on the dose of 32 mg until the present period of follow-up lasting for 16 months.

DISCUSSION

The MRI findings may be similar to other inflammatory, infectious or neoplastic disorders, such as multiple sclerosis, malignancy or lymphomatoid granulomatosis of the CNS, primary cerebral angiitis, paraneoplastic encephalitis, neuromyelitis optica, connective tissue diseases, systemic T cell lymphoma and Hodgkin's lymphoma. We performed detailed additional tests to exclude other potential causes and to fulfil this diagnostic criterion (Tobin et al., 2017; Zalewski and Tobin, 2017).

We observed immediate and significant improvement after intensive steroid treatment. Such response to steroids is a characteristic feature of CLIPPERS, but some patients may not reach the full recovery, as was the case of our patient (Taieb et al., 2012). We observed clinical and radiological improvement. Therapeutic recommendations suggest initial intravenous methylprednisolone at doses of 1,000 mg

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for 5 days continued with oral steroids and subsequent steroid-sparing drugs, such as methotrexate, mycophenolate mofetil, hydroxychloroquine, cyclophosphamide or azathioprine (Gabilondo et al. 2011; Tobin et al., 2017). There are reports on good clinical response to leflunomide treatment (Didier et al., 2018; Veerapandiyan et al., 2017). Long-term effectiveness of anti-CD20 monoclonal antibody (rituximab) was also reported (Cipriani et al., 2018). The optimal duration of treatment is not known due to the low prevalence of CLIPPERS. To our knowledge, there had been two patients diagnosed with this disorder and described in Poland before (Bladowska et al., 2017; Papier et al., 2018). The median age at onset is 58 years, but there was a report of a 10-year-old girl (Tobin et al., 2017; Veerapandiyan et al., 2017).

Our patient may be diagnosed with probable CLIPPERS according to Tobin et al. (2017). We fulfilled all clinical criteria: subacute pontocerebellar dysfunction with a cognitive dysfunction, responsiveness to steroids, absence of peripheral nervous system disease and the lack of alternative better explanation for clinical presentation. We also observed 3 of 4 radiological criteria: (1) homogenous, gadolinium enhancing nodules without ring enhancement and mass effect with predominant localisation in the cerebellum and pons, measuring <3 mm in diameter; (2) marked improvement in enhancement after steroid treatment; (3) homogenous T2-signal abnormality where the degree of these lesions does not significantly exceed the size of the enhanced area. We did not reveal any lesions in the spinal cord (the fourth radiological criterion), and did not perform neuropathological examination. The CSF analysis was normal and no oligoclonal bands were found; however, mild elevation of protein or pleocytosis may be observed (Tobin et al., 2017).

The main goal for the future considerations regarding CLIPPERS are the guidelines for the differential diagnosis including proper selection of cases where brain/brainstem biopsy may be needed. Another important issue is the optimal type and duration of treatment, especially taking into consideration the adverse effects of chronic immunosuppressive treatment.

Conflict of interest

Authors declare no conflict of interest.

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