Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) syndrome: Treatment approach depends on disease course

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Introduction. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare inflammatory central nervous system (CNS) disorder, chiefly involving the brainstem, especially the pons. The diagnosis is challenging, requires careful exclusion of alternative diagnoses and a targeted therapeutic approach. CLIPPERS is known to respond well to corticosteroids, but the treatment needs to be long-term and can cause significant side-effects. Moreover, subsequent corticosteroid withdrawal often leads to a relapse. It has been suggested that anti-CD20 molecules could benefit several antibody-mediated CNS inflammatory diseases, including CLIPPERS.
Case report. This paper describes two cases of CLIPPERS. The first demonstrates the benefit of early introduction of corticosteroids with side effects in cases of long-term use. The second demonstrates the efficacy of ocrelizumab (anti-CD20 molecule) in a severe course of CLIPPERS.
Conclusion. These two cases bring attention to this rare, often misdiagnosed but treatable disease.

Key words: CLIPPERS, ocrelizumab, corticosteroids, autoimmune disorders, brainstem

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INTRODUCTION

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a rare inflammatory autoimmune disorder of the central nervous system (CNS) characterized mainly by pontocerebellar symptoms, myelopathy, and excellent response to corticosteroids (CS). Small punctiform gadolinium enhancing MRI lesions are usually localised in the brain stem and spinal cord[1].These lesions (unlike multiple sclerosis lesions) are punctate and curvilinear, "peppering" the pons and adjacent rhombencephalic structures such as the cerebellar peduncles, cerebellum, medulla, midbrain and occasionally the spinal cord[1,2]. They lack the ring enhancement or mass effect, and are often less than 3 mm in diameter[1,2]. CS treatment decreases lesion activity which is reflected in reduced enhancement.

Histopathological analyses present perivascular and parenchymal T cell lymphocytic infiltrates in both white and grey matter (predominantly CD4) while macrophages vary. Absence of myelin loss, either primary or secondary, as well as lack of other alternative brain pathology seem to be typical for CLIPPERS[1,2]. In the absence of histopathology results, the patient fulfilling all other criteria is diagnosed with probable CLIPPERS.

Current knowledge and experience favour corticosteroid treatment. However, there are adverse side-effects of long-term CS therapy and relapses after CS withdrawal. Use of other immunosuppressive treatments have been reported only occasionally[1,3-6]. With so few reported cases, it has not been possible to establish recommendations for diagnostics and therapy for CLIPPERS[1-3].

Here we present our experiences with two different treatment approaches to the CLIPPERS syndrome, depending on the disease course.

CASE 1

A 47-year-old man with a history of arterial hypertension was admitted to our clinic on January 2017. He presented a 2-week history of sustained dizziness, gait instability and blurred speech. These symptoms were preceded by mild influenza with joint and muscle pain, runny nose but without a need of any specific treatment.

The physical examination revealed dysarthria without affecting the bulbar system, horizontal left beating nystagmus grade 3, right-sided facial hypoesthesia, left ataxic hemiparesis, exaggeration of stretch reflexes and ataxic gait, with positive Romberg sign. Meningeal symptoms were negative, general clinical examination was normal.

Brain computed tomography (CT) including CT angiography of the cerebral arteries performed at the time of admission was normal.

Examination of cerebrospinal fluid (CSF), performed on the same day, showed moderate increase in

the concentration of proteins (0.530 g/L; normal range: 0.150–0.450 g/L) with no evidence of oligoclonal bands; the level of glucose, lactate, and cell count were normal. CSF antigen and antibody tests for neuroinfectious agents were negative.

Serology tests were negative for HIV, syphilis, borrelia, varicella zoster, cytomegalovirus, herpesvirus family, and hepatitis B and C viruses.

Brain T2-weighted FLAIR magnetic resonance imaging (MRI) showed diffuse patchy hyperintensity of the pons, the middle cerebellar peduncles, and cerebellar hemispheres (Fig. 1A). T1-weighted post gadolinium scans displayed multiple punctate enhanced foci in perivascular area, involving the pons and adjacent midbrain, medial parts of the middle cerebellar peduncles (Fig. 1B). Other sporadic enhanced foci were also found within the cerebellar hemispheres. There was no evidence of leptomeningeal enhancement, and the MRI of the spinal cord was normal. Axial DWI and relative ADC map did not reveal any focal areas of restricted signal.

A whole-body CT scan was conducted to rule out lymphomatous, inflammatory, systemic, or tumoral diseases. Onco-neuronal and antinuclear antibodies were negative. Tumour markers were within the normal range, except for slightly increased levels of CA72-4. No oncological disease was detected.

The treatment started with intravenous methylprednisolone 1 g/day for 5 days and was followed by decreasing doses of oral prednisone, starting at 1 mg/kg/day together with 100 mg of azathioprine per day. All the initial symptoms completely subsided within 48 h.

One month later, the patient returned to our clinic for a follow-up consultation. At that time, the prednisone dose was 0.5 mg/kg/day. This time, brain and spinal cord MRI revealed no punctiform hyperintense lesions and no gadolinium-enhancing lesions (Fig. 2).

As other potential diseases were ruled out, the patient was diagnosed with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS syndrome).

Oral methylprednisolone dose was gradually tapered over the next six months. However, once his dose of oral methyprednisolone was on 10 mg per day, he experienced recurrent gait ataxia and MRI revealed new lesions. Based on the results, the patient received new pulse of CS therapy (intravenous methylprednisolone 1000 mg/day in three subsequent days) followed by an increased dose of oral methylprednisolone 20 mg/day with 100 mg azathioprine. He remained stable for 1 year, so we reduced the dose of methylprednisolone. However, once his dose of methylprednisolone was under 10 mg per day, the patient again developed clinical relapse with radiological worsening, and were completely resolved by another CS therapy (methylprednisolone 1000 mg/day × 5). Subsequently, his daily dose of azathioprine was increased to 150 mg per day and the dose of oral methylprednisolone was gradually tapered over the next year. His current treatment is 5 mg of methylprednisolone with azathioprine 100mg per day and his clinical and radiological status is stable. However, the treatment has adverse side effects. The patient developed steroid diabetes mellitus, weight gain, and arterial hypertension.

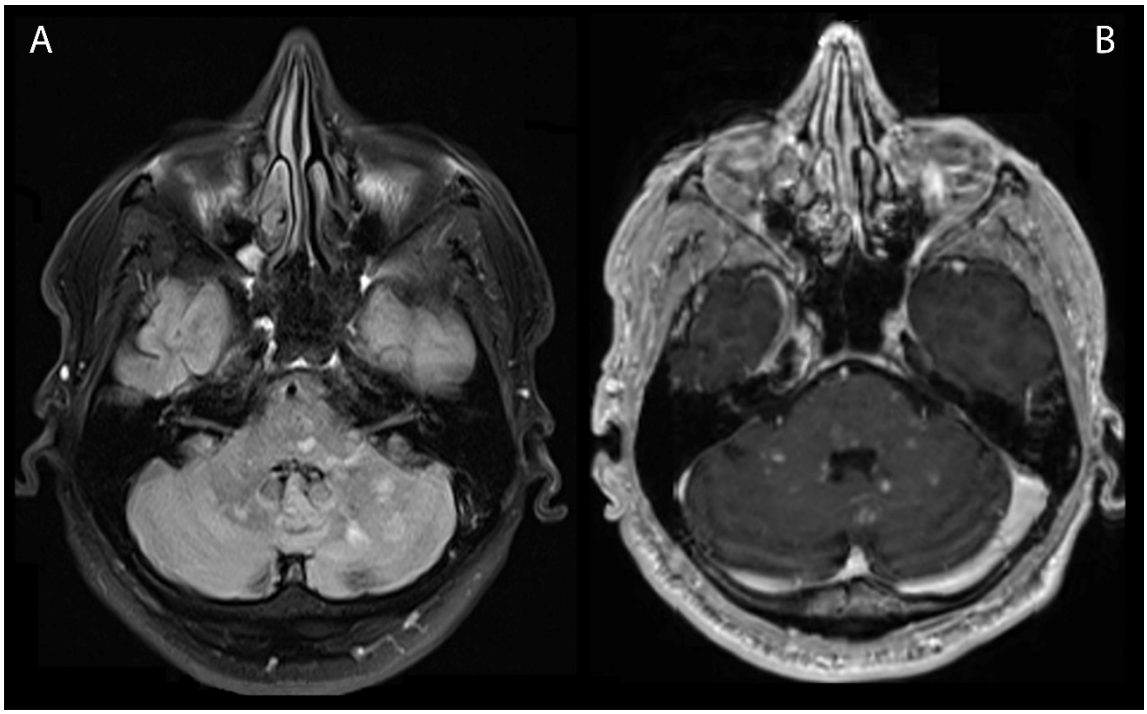

Fig. 1. Pre-treatment Case 1, Axial T2-weighted FLAIR brain MRI scan obtained in a 3T scanner at the time of diagnosis before treatment onset. **A.** The image shows numerous hyperintense punctiform lesions measuring <3 mm in diameter ("salt and pepper sign"), predominantly in the infratentorial region (affecting the middle cerebellar peduncles and pons). **B.** Homogeneous gadolinium enhancement in all punctiform lesions (post-gadolinium T1w).

CASE 2

A 25-year-old man diagnosed with probable CLIPPERS in November 2019, with the first neurological symptoms possibly suggesting the disease in December 2016 at the age of 20.

Between December 2016 and January 2019, he experienced several relapses with brain stem symptoms (diplopia, right facial nerve palsy, gait, and limb ataxia, left side hemihypesthesia). First MRI examination showed small hyperintense lesions of the pons and mesencephalon, to a lesser extent in both thalami, cerebellar peduncles, cerebellar hemispheres (Fig. 3A, 3B), and in the spinal cord.

Examination of CSF showed moderate increase in the concentration of proteins (0.64 g/L; normal range: 0.150–0.450) with no evidence of oligoclonal bands; the cell count as well as a level of glucose and lactate were normal. CSF antigen and antibody testing for infectious agents were also negative.

The treatment started with CS pulse therapy. Due to recurrent relapses, the pulse therapy was repeated several times over the next 3 years. Follow-up post CS treatment MRI examinations showed regression of T2/FLAIR hyperintense lesions in thalami, pons, cerebellar hemispheres, and spinal cord, which was only temporary.

Each time CS treatment alleviated the symptoms within several days, but they did not return all the way to the previous level, and so neurological deficit slowly increased over time.

In contrast to Case 1, the patient was not continually on CS or other immunosuppressive medication between relapses due to risk of secondary complications.

In November 2019, his disease progressed again, and his brainstem symptoms worsened significantly (severe dysarthria and dysphagia; progressed cerebellar ataxia and left side hemihypesthesia).

Repeated analysis of the CSF revealed mildly increased protein levels (0.73g/L: 0.150–0.450). Other biochemical parameters were normal included cell counts. There was no evidence of oligoclonal bands in CSF again. The broad differential diagnosis (including CNS lymphoma, primary CNS vasculitis, neuromyelitis optica spectrum disorders, paraneoplastic syndromes, autoimmune encephalitis, sarcoidosis, tuberculosis and neurolues) was negative. Serum anti-neuronal antibodies, anti-ganglioside antibodies, antibodies against aquaporin 4 receptor (AQP4), against anti myelin oligodendrocyte glycoprotein (MOG), anti-myelin associated protein (MAG), antiphospholipid antibodies, antinuclear antigen and antineutrophil cytoplasmic antibodies (ANA and ANCA) were negative.

Multiparametric MRI examination (Jan 2020) of the brain excluded other brain disorders. PET CT of chest did not find pathological enlargement of lymph nodes and granulomatous pulmonary disease.

In March 2020, the patient started treatment with ocrelizumab as he was first diagnosed as multiple sclerosis. Repeated MRI scans and retrospective clinic-radiological analysis and after a course of 19 months, he has not had any new relapse and his neurological status improved

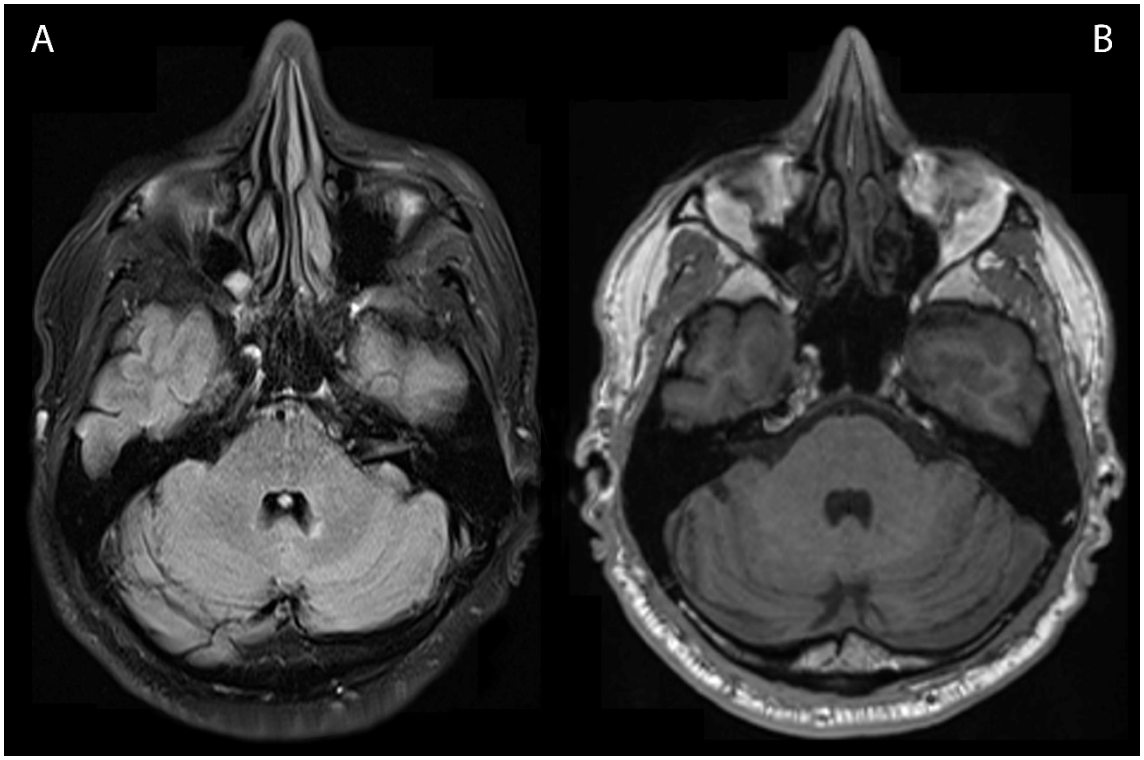

Fig. 2. Post-treatment Case 1. Axial T2-weighted FLAIR brain MRI scan obtained 1 month after steroid treatment onset. **A.** MRI examination shows a significant reduction in number and size of hyperintense lesions in the infratentorial region. **B.** With a complete regression of enhancing lesions in cerebellar hemispheres and peduncules.

(mild dysarthria, dysphagia, and cerebellar ataxia, no hemihypesthesia). After starting the treatment, the MRI showed reduction of brain stem lesions (Fig. 3C, 3D).

DISCUSSION

According to the proposed diagnostic criteria for CLIPPERS syndrome, the presented patients fulfilled clinical and radiological criteria of the disease without available neuropathology[2]. We did not decide for a biopsy of brainstem tissue due to the risk of complications and good clinical and radiological responsivity to CS. In the second patient, additional laboratory and repeated advanced MRI examinations did not give rise to suspicion of neoplasia or other than neurological diseases.

Clinical practice shows that the CLIPPERS syndrome responds rapidly to CS therapy. The currently favoured treatment is based on methylprednisolone boluses dosed at 1 g/day for 3–5 days, followed by maintenance treatment with methylprednisolone dosed at 1 mg/kg/day. The optimal duration and the rate of reduction of maintenance doses has not been established so far[1,2,7].

In the case of our first patient, we were trying to establish the most efficient course of CS maintenance treatment to avoid adverse side effects. So far, we have

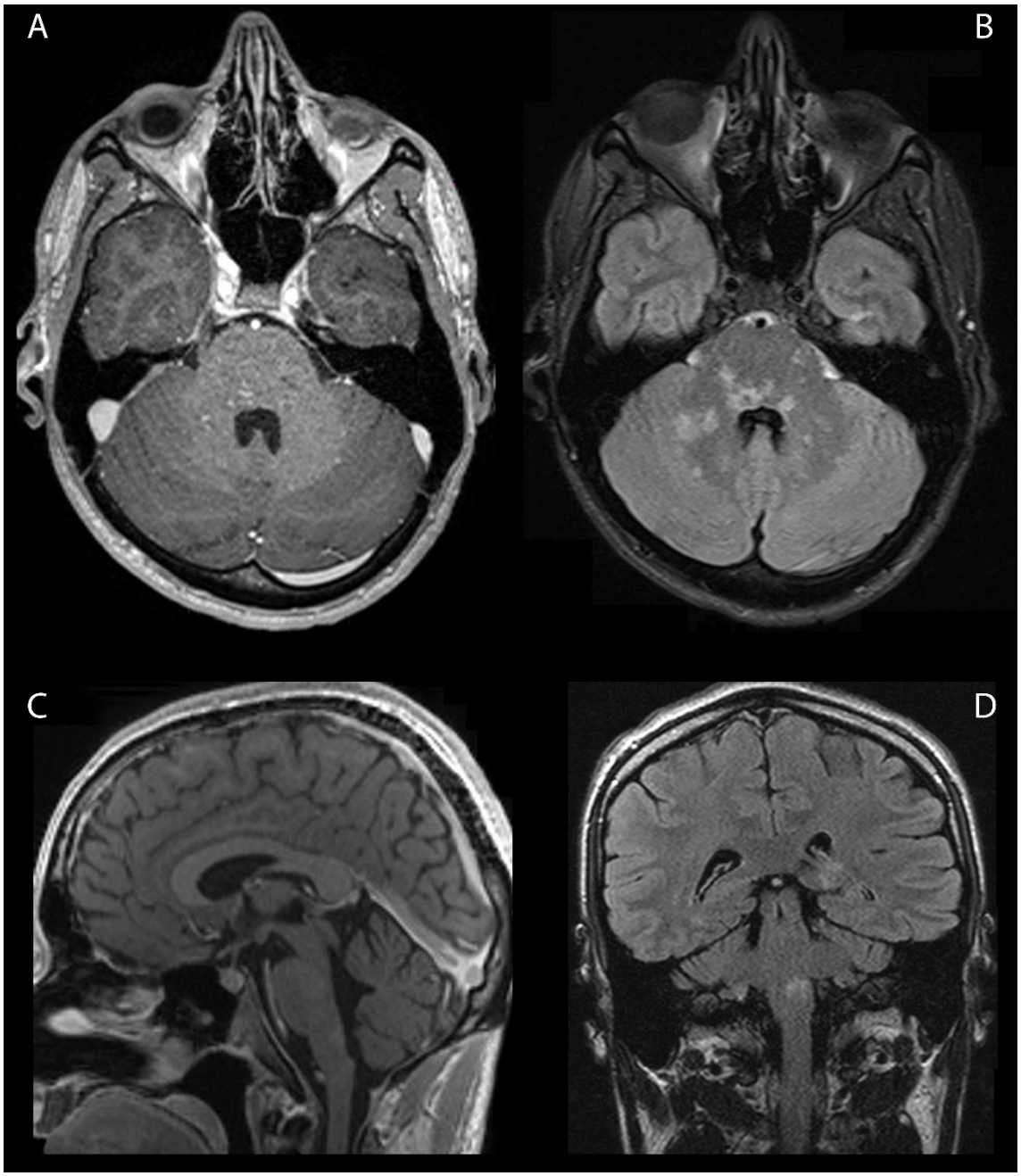

Fig. 3. Case 2. **A.** Transversal brain FLAIR MRI showes small patchy hyperintensities of the pons and mesencephalon, to a lesser extent in both thalami, cerebellar peduncles and cerebellar hemispheres. **B.** Transversal T1 brain stem Gd+ hyperintensities. **C.** Sagital T1 MPR brain stem with residual nonenhancing lesions after ocrelizumab treatment. **D.** Coronal T1 with a residual lesion in medulla oblongata after ocrelizumab treatment.

not been able to stop immunosuppressive treatment. Moreover, we did not avoid side effects.

As therapeutic recommendations of CLIPPERS have not been fully established yet our knowledge is based on experience. It is hypothesised, azathioprine or other immunosuppressive drugs might have been as effective as CS to maintain remission[5,8], and corticosteroid-sparing agents are aimed at to reduce the dose of corticosteroids[5,8,9]. However, most patients use oral CS alone[5,10]. Some authors[9] reported superiority of azathioprine over CS, presenting improvement of clinical and radiological parameters after follow-up examinations. Gabilondo et al.[11] attempted to taper CS to 5 mg/ day and to use intravenous immunoglobulins (0.4 g/kg/day for 5 days) for a patient, but the patient's symptoms reappeared in 2 days after administering the last dose of intravenous immunoglobulins. Taieb et al.[5] observed 42 relapses among 12 patients in a mean follow-up period of 5.5 years. Relapses are provoked by withdrawing or tapering CS below a lower dose limit. The duration of treatment is unclear. Although long-term CS treatment seems necessary for most patients with CLIPPERS, there were reported rare cases of patients needed other immunosuppressive treatment. Methotrexate, mycofenolate mofetil, cyclophosphamid and antireumatics hydrochlorochine were the most common[2,5]. Few reports described effectivity of anti-CD20 molecule rituximab in treatment of CLIPPERS[12,13], and only one work presented experiences with short-lasting ocrelizumab treatment[14].

In the case of our second patient, effective maintenance treatment might have been beneficial, but we did not prescribe it due to uncertain diagnosis. The repeated relapses responded to further boluses of methylprednisolone only temporarily and over time they caused permanent neurological deficit. With the benefit of hindsight, steroid-sparing agents may have been a better option[10,15]. However, after starting treatment with ocrelizumab, the patient improved, and progression of the disease stopped. Repeated MRI scans and retrospective clinic-radiological analysis led to the diagnosis of CLIPPERS. Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B cells causing their depletion. A theory that B cells are important regulators of T-cell activity and B cells are involved in T-cell antigen presentation and co-stimulation, can help explain the effectivity of B-cell depletion therapy in the case of our second patient[12-14]. In contrast to rituximab (chimeric monoclonal antibody targeted against CD20-B cells) (ref.[12,13]) reported occasionally in treatment of CLIPPERS, ocrelizumab should have less intensive adverse effects and risks. This work is second to present treatment with ocrelizumab in the case of probable CLIPPERS. In the first presented, Mehta et al.[14] hypothesised that B-cell depletion therapy might change the proportion of T-cells that produce inflammatory cytokines, thus decreasing the ability for T-cells to cause inflammation. However, the authors did not show any superiority of anti-CD20-B cell therapy over dual anti-T and B-cell depletion using azathioprine. Moreover, the authors are of the opinion that, targeted B-cell treatment for patient with CLIPPERS should not be generally recommended. Long-term monitoring of MRI and clinical markers in the patient treated by B-cell targeted immunomodulatory treatment is needed.

In our patient, we have not found evidence for the absence or secondary myelin loss in probable CLIPPERS[2]. We have assumed that the course of the disease and residual neurological deficit depend on intensity and timing of immunomodulatory treatment. The same is true for other inflammatory demyelinating CNS disorders.

CONCLUSIONS

Our cases present different courses of probable CLIPPERS and different treatment approaches. Our second case is the second to demonstrate the efficacy of ocrelizumab in the severe course of CLIPPERS. The efficacy of ocrelizumab (humanised monoclonal antibody against CD-20 B cell) in the treatment of CLIPPERS syndrome supports the role of B cells as important regulators of T-cell activity in the disease. However, controversies about the treatment effectiveness remind us of the need for constant vigilance.

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