CASE REPORT

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Glioblastoma mimicking Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) syndrome – case Report

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Abstract

Non-specific focal lesions in the central nervous system pose diagnostic and therapeutic challenges. Moreover, the prognosis, depending on the lesion etiology, can be extremely varied from mild and potentially curable to extremely severe and untreatable lesions. Interestingly, due to the lack of a definitive diagnosis, the patient frequently remains in observation until the disease progresses. This case study presents a patient in whom the radiological image of a non-specific brainstem lesion was consistent with glioblastoma mimicking Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids syndrome (CLIPPERS). Radiologically compatible CLIPPERS may conceal a number of different pathologies. Reports of CLIPPERS mimickers highlight the importance of considering alternative diagnoses in patients presenting with the CLIPPERS phenotype. The clinical and radiologic presentation of glioblastoma with features mimicking CLIPPERS are described.

Key words

CLIPPERS, Glioblastoma, Oncology

INTRODUCTION

Non-specific focal lesions in the central nervous system pose diagnostic and therapeutic challenges. Moreover, the prognosis, depending on the lesion etiology, can be extremely varied ‑ from mild and potentially curable to extremely severe and untreatable lesions. Interestingly, due to the lack of a definitive diagnosis, the patient frequently remains in observation until the disease progresses. This case study presents a patient in whom the radiological image of a non-specific brainstem lesion was consistent with glioblastoma WHO grade IV mimicking Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids syndrome (CLIPPERS) [1].

CASE REPORT

A 26-year-old man was admitted to the Department of Neurology due to progressing paresis of his left extremities with associated speech impairment. The patient had remained in observation at the outpatient clinic for 3 months due to a non-specific brainstem lesion. During the observation period, he had contracted COVID-19 which gave scarce symptoms. The COVID-19 pandemic may have delayed the diagnostic process, which resulted in the lesion expanding. On admission to the Department, the neurological examination revealed dysarthria, left extremity paresis (grade 3 according to the Lovett Scale: muscle strength reduced to such an extent that the joint could be moved only against gravity with the examiner's resistance completely removed) and positive pyramidal signs (Babinski, Rossolimo) on the left side, without other abnormalities. The medical history of the patient and his family were unremarkable. MRS examination showed that the lesion encompassed almost the entirety pons, in particular right part of the pons. Contrast enhancement showed smal and diffuse disorganized nodules. A second MRS 1.5 months later showed slight progression in the size of the lesion (Fig. 1). The imaging study with contrast enhancement showed a greater degeree of the small, diffuse and unorganized nodules in the pons. The subsequent head MR examination showed the progression of the described lesion with a non-specific nature. However, this was most likely consistent with CLIPPERS syndrome, due to multiple foci of punctate pontine enhancement (peppering) suggestive of perivascular distribution (Fig. 2).

Laboratory tests, which included a complete blood Mount, were not within normal limits. White blood cells (WBC) and neutrocytes (NEU) were higher, Chile lymphocytes (LYMPH), eosinophils (EOS), basophils (BASO) and mean platelet volume (MPV) were lower than normal. Lactate dehydrogenase (LDH), however, was normal. Examination of cerebrospinal fluid showed that it contained proteins higher

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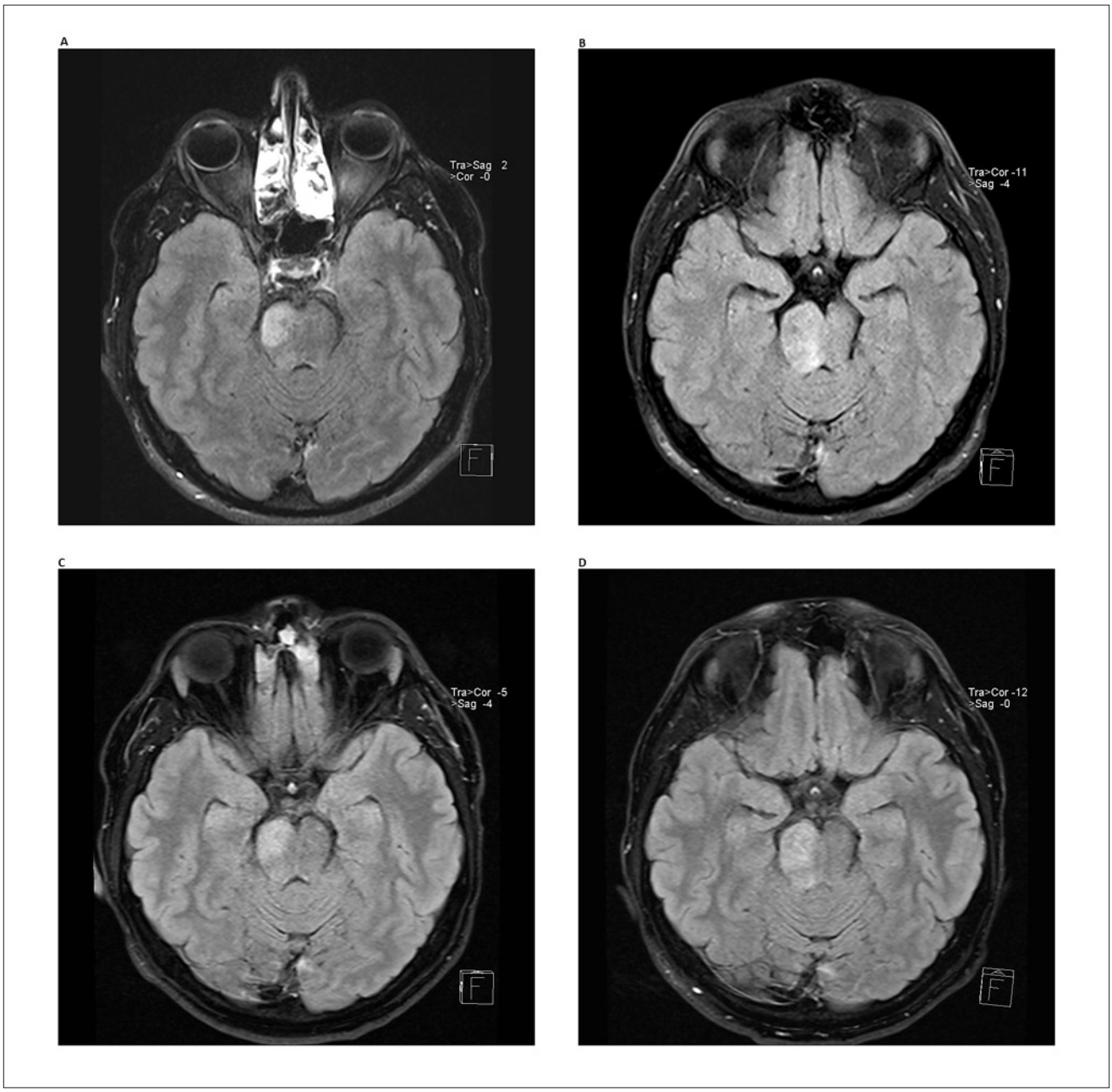

Figure 1. The MRS examination showed the lesion encompassed pons (A, B) and the second MRS after 1.5 months later showed slight progression in the size of the lesion (C,D)

then normal limits (98 mg/dl), but other parameters were normal. Protein fraction pattern were within normal limits and oligoclonal bands were not detected. Cerebrospinal fluid cultures were negative and contained atypical cells revealed in cytologic evaluation. Anti-neutrophil cytoplasmic antibodies: c-ANCA (anti-proteinase-3 antibodies PR3) and p-ANCA (myeloperoxidase antibodies MPO) were negative. The patient was disqualified from biopsy several times by the consulting neurosurgeon, whose decision stemmed from concerns related to the challenging location of the lesion. Extensive laboratory diagnostics, in the context of vasculitis or lymphoma, did not yield any new data.

Meanwhile, the patient's condition deteriorated spectacularly: plegia developed on the left side of his body, coupled with glossopharyngeal, facial and sublingual nerve paralysis on the right side. Based on the entire clinical image, the decision was made to start empiric steroid treatment (1,000 grams of Solu-Medrol for 5 days, without complications). However there was no improvement or stabilization of the patient's clinical condition. Subsequently, following an external consultation with the Neurosurgery Centre at the Military Hospital in Bydgoszcz, the decision was made to perform a brainstem biopsy. The neurosurgeons used an infratentorial approach in stereotactic biosy, a procedure that was performed without complications. Histopathological examination presented glial cells derivatives with atypical cells, which had polymorphic and hyperchromatic nuclei with figures of cell divisions, but with no necrotic components. The result of the histopathological examination showed the presence of glioblastoma cells (World Health Organization, grade G4). Immunohistochemically, the tumour cells were reactive for the glial-fibrillary-acid-protein GFAP, MIB-1

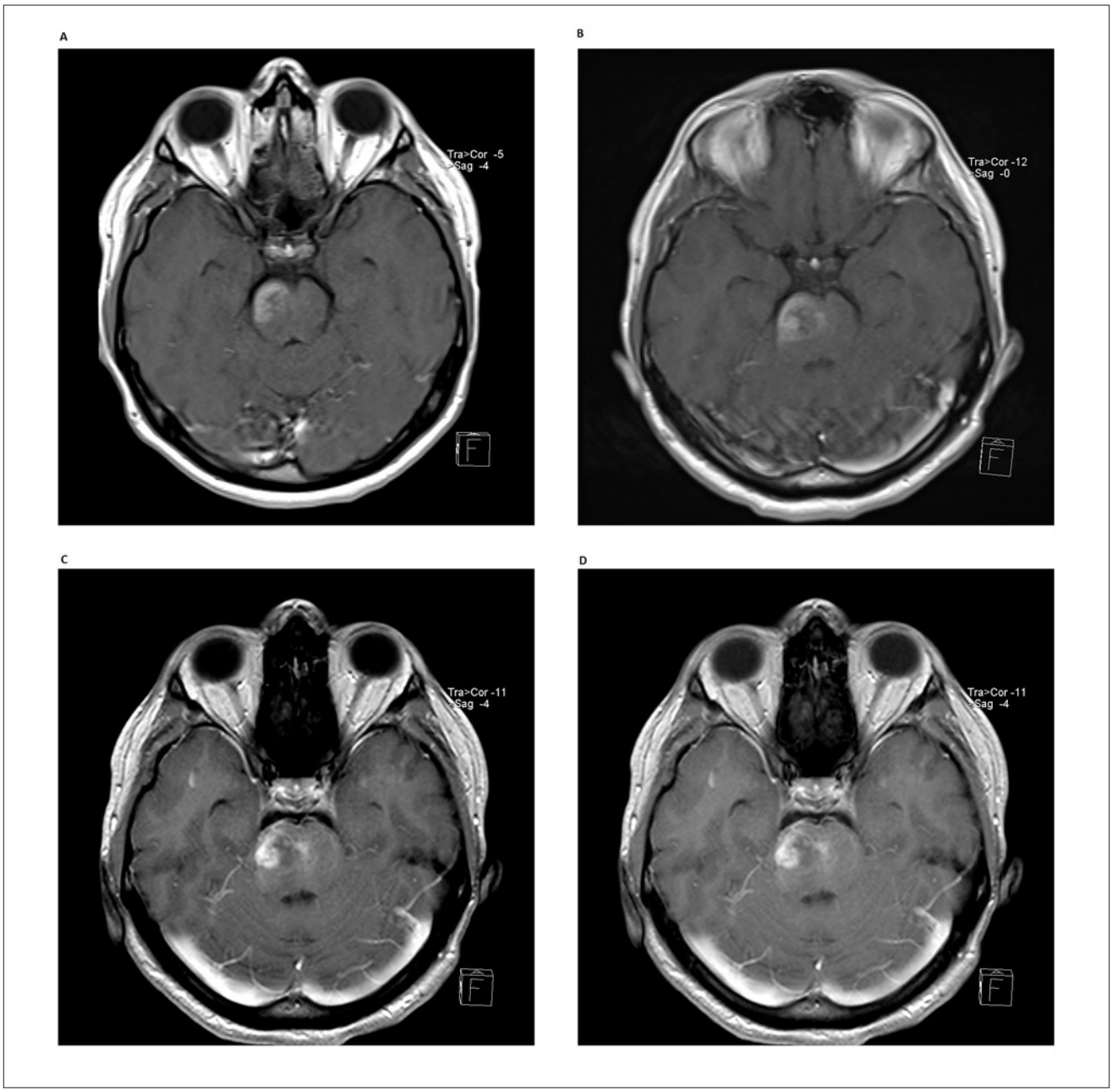

Figure 2. The first CNS MR examination (A, B) and the second MR examination after progression (C,D)

(focal in 10% tumour cells), synaptophysin and LAC (in small lymphocytes of the inflammatory infiltrate). The following were negative: AE1/AE3. The patient was disqualified from further oncologic treatment and radiotherapy due to his severe clinical condition.

DISCUSSION

The case study presents a case of misdiagnosis which caused delay in treatment and complication. The aim was to familiarise CLIPPERS, a rare disease or rather its symptoms. CLIPPERS has only recently been defined and to-date has received only limited attention. The diagnosis of CLIPPERS is challenging, and requires careful exclusion of alternative diagnoses. No specific serum or cerebrospinal fluid (CSF) biomarker for the disorder is currently known. CLIPPERS is characterized by subacute brainstem signs and symptoms, punctated by curvilinear enhancing lesions mainly involving the pons, which may extend to adjacent structures, prompt clinical and radiological steroid sensitivity, and the absence of alternative diagnosis [2].

In clinical practice the most urgent and perplexing problem is how to eliminate other similar manifesting diagnosis, such as lymphomas, gliomas or vasculitis [3]. Diagnosis is achieved based on clinical, radiological and pathological presentation [4]. Both in the original study and many other subsequent studies, the patient mainly presented with ataxia, diplopia, long-track signs, and dysarthria that evolve over weeks or months [5]. Typical offset occurs during midlife, but there is no documented preference for either age or gender of the patients [5, 6]. The inflammation typically includes

perivascular spaces in the pons or cerebellum, but it may occur in other localizations, such as the spinal cord, midbrain and medulla [7, 8]. Pathogenesis of CLIPPERS is still not clear and many theories are being investigated for verification [6].

In many cases that occurred, some suggested an autoimmune background involving lymphocytes T helper 17 [9]. The basics of diagnosis are physical examination and neuroimaging, as well as serological evaluation, cerebrospinal fluid analyses (CFS), laboratory tests and lesion biopsy in atypical casus, in order to exclude other diagnosis [2, 4, 5, 8, 10]. Blood count, liver and renal screening tend to remain within normal values. The most common finding in CFS is a mild elevation of protein [5, 8, 11]. Major findings verifying diagnosis are found in the MRI punctate and curvilinear enhancement peppering the pons, with the lesions being gadolinium dependent [3, 8]. In most casus, punctate lesions can occur in other locations but their intensity decreases with distance from the pons and cerebellum [12]. However there have been cases with other non-specific changes, mainly in the T-2 sequence [11]. Studies have indicated that nodular enchantment should be treated more like an atypical presentation than a red flag [13, 14]. Corticosteroid responsiveness is one of the diagnosis criteria. Most frequent approach is methylprednisolone 1g daily for 5 days intravenous or dose 20–60 mg oral per day [8]. Studies show that high doses of steroids (>20mg daily) for long time therapy can prevent relapse [1]. Methotrexate and azathioprine may be useful in this diagnosis [17].

After considering all the studies and casus, there are still no clear guidelines for diagnostics. In order to ensure the diagnosis, every patient with red flags or atypical presentation should have a stereotactic brain biopsy conducted [15, 16]. Also, patients whose lesions do not respond to treatment should have a biopsy performer [16]. The most common findings in the biopsy are lymphocytic inflammation with perivascular predominance and parenchymal diffuse infiltration [8]. Dominant cells are CD-3 positive lymphocytes and lymphocytes B, with the dominant type being lymphocytes CD-4 positive rather than CD-8 positive. Furthemore, in the light of the recent COVID-19 pandemic, new reports have linked CLIPPERS with SARS-CoV-2 complications. COVID-19 may indicate many clinical pathologies involving the central nervous system [18].

CLIPPERS is rare autoimmunological syndrome, difficult to associate with any other condition; however, this is possible and needs further research as CLIPPERS Has occurred following other viral diseases [19]. Some authors have found a connection between CLIPPERS and Epstein- Barr Virus (EBV) [10].

CONCLUSION

In conclusion, radiologically compatible CLIPPERS may conceal a number of different pathologies. Reports of CLIPPERS mimickers highlight the importance of considering alternative diagnoses in patients presenting with the CLIPPERS phenotype. This case report described the clinical and radiologic presentation of glioblastoma with features mimicking CLIPPERS. In the presented case, the diagnosis was achieved through a contrast MRI of the brain, suggestive of CLIPPERS syndrome. However, the patient's CNS symptoms did not improve after glucocorticoids therapy. Hence, the lack of response to steroid therapy was considered indicative of a different diagnosis. For further clarification of the lesion, a brain biopsy was performed. After biopsy, the histopathologic diagnosis revealed glioblastoma. Only conducting a brain biopsy resulted in the correct and definitive diagnosis. This difficult case with untreatable cancer and unclear symptoms caused a delay in the treatment, causing complications and poor prognosis for the patient.

Clinicians and radiologists should be aware of this condition and its differential diagnoses, given that CLIPPERS constitutes a treatable condition and that patients may benefit from an early introduction of GCS as a result of long-term immunosuppression. Considering the uncomplicated therapeutic options, the most important for the patent is a prompt and accurate diagnose and implementation of therapy, which in this case, however, presented difficulties, which may not be so obvious in some cases.

When CLIPPERS is observed, it is crucial to test for mimickers. Despite considering all the studies and cases, there are still no clear guidelines for diagnostics, in order to ensure correct diagnosis in every patient with red flags or atypical presentation. Therefore, these patients should have a stereotactic brain biopsy performer [15, 16]. Also, patients in whom lesions did not respond to treatment should have a biopsy conducted [16]. Many red flags and uncertain until treatment diagnosis makes it even more important for clinicians to improve the criteria and diagnostic process, as diseases mimicking CLIPPERS are much more common than may occur**.** Further studies are necessary to determine the exact potential biomarkers as well as the reliable diagnostic criterias.

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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Patient consent
Informed, written consent was obtained from the patient.

REFERENCES

1. Zalewski NL, Tobin WO. CLIPPERS. Current Neurology and Neuroscience Reports. 2017 Sep;17(9):65. doi: 10.1007/s11910-017-0773-7. PMID: 28726127.
2. Taieb G, Allou T, Labauge P. Therapeutic Approaches in CLIPPERS. Curr Treat Options Neurol. 2017 May;19(5):17. doi: 10.1007/s11940-017-0455-4
3. Pittock SJ, Debruyne J, Krecke KN, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Brain. 2010;133(9):2626–2634. doi:10.1093/brain/awq164
4. Axelerad A, Stroe A, Mihai C, et al. CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids: A challenge in neurological practice, clinical landmarks (Review). Exp Ther Med. 2021;22(4):1191. doi:10.3892/etm.2021.10625
5. Zalewski NL, Tobin & WO. DEMYELINATING DISORDERS (J BERNARD AND M CAMERON, SECTION EDITORS) CLIPPERS. Published online 1910. doi:10.1007/s11910-017-0773-7

6. Zhang L, Zhao D, Li J, et al. A case report of CLIPPERS syndrome and literature review. Medicine (Baltimore). 2021;100(22):e26090. doi:10.1097/MD.0000000000026090
7. Vola E, Russo C, Macera A, et al. Unusual CLIPPERS presentation and role of MRI examination in the proper diagnostic assessment: A case report. Eur J Radiol Open. 2019;6:212–214. doi:10.1016/j.ejro.2019.05.005
8. Tobin WO, Guo Y, Krecke KN, et al. Diagnostic criteria for chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Brain. 2017;140(9):2415–2425. doi:10.1093/brain/awx200
9. Mélé N, Guiraud V, Labauge P, et al. Clinical/Scientific Notes effective antituberculous therapy in a patient with clippers: New Insights Into Clippers Pathogenesis. 2014;1:6. doi:10.1212/NXI.0000000000000006
10. Dang YL, Kuan Kok H, Mckelvie PA, et al. Chronic lymphocytic infiltration with pontine perivascular enhancement responsive to steroids (CLIPPERS) and its association with Epstein-Barr Virus (EBV)-related lymphomatoid granulomatosis: a case report. 2021;doi:10.1186/s12883-021-02110-1
11. Gul M, Chaudhry AA, Chaudhry AA, et al. Atypical presentation of CLIPPERS syndrome: A new entity in the differential diagnosis of central nervous system rheumatologic diseases. J Clin Rheumatol. 2015;21(3):144–148. doi:10.1097/RHU.0000000000000238
12. Berzero G, Taieb G, Marignier R, et al. CLIPPERS mimickers: relapsing brainstem encephalitis associated with anti-MOG antibodies. Eur J Neurol. 2018;25(2):e16-e17. doi:10.1111/ene.13483
13. Rauschenbach L, Kebir S, Radbruch A, et al. Challenging Implications of Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids Syndrome with an Atypical Presentation: Report of Two Cases. World Neurosurg. 2020;143:507–512. e1. doi:10.1016/j.wneu.2020.07.123
14. Taieb G, Mulero P, Psimaras D, et al. CLIPPERS and its mimics: evaluation of new criteria for the diagnosis of CLIPPERS. J Neurol Neurosurg Psychiatry. 2019;90(9):1027–1038. doi:10.1136/jnnp-2018-318957
15. Galazky I, Büntjen L, Voges J, et al. Brain biopsy in patients with CLIPPERS syndrome: why and when. Ther Adv Neurol Disord. 2022;15:175628642110628. doi:10.1177/17562864211062821
16. Ge N, Julien L, Oana P, et al. Brain biopsy is required in steroid-resistant patients with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). 2011; doi:10.1007/s11060-011-0724-0
17. Taieb G, Duflos C, Renard D, et al. Long-term outcomes of CLIPPERS (Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids) in a consecutive series of 12 patients. Arch Neurol. 2012;69(7):847–855. doi:10.1001/archneurol.2012.122
18. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19(9):767–783. doi:10.1016/S1474-4422(20)30221-0
19. Wang L, Holthaus EA, Jimenez XF, et al. MRI evolution of CLIPPERS syndrome following herpes zoster infection. J Neurol Sci. 2015;348(1–2):277–278. doi:10.1016/j.jns.2014.11.022