Annals of Medicine and Surgery 79 (2022) 104040

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Case Report

Right arm weakness and mouth deviation as a presentation of Primary Angiitis of the Central Nervous System treated with rituximab: A case-report

Fajr MA. Sarhan [a,*], Ameer Al-Jasim [b], Rami SN. Alaraj [a], Safwan FA. Abedalkhader [a,c], Zaid Ghanim [a,c]

[a] Al-Quds University-School of Medicine, Abu-Dis, East Jerusalem, West Bank, Palestine
[b] College of Medicine-University of Baghdad, Baghdad, Iraq
[c] Internal Medicine department, Palestine Medical Complex, Ramallah, West Bank, Palestine

ARTICLE INFO

Keywords:
Primary Angiitis
Central Nervous System
Vasculitis
Literature review
Case report

ABSTRACT

Introduction: Primary Angiitis of the Central Nervous System (PACNS) is a rare form of vasculitis that solely affects the Central Nervous System (CNS). Its presentation varies widely from a simple headache to a stroke-like presentation. PACNS management is divided into an induction phase, which includes corticosteroids, cyclophosphamide and rituximab, and a maintenance phase which includes: methotrexate, mycophenolate mofetil, rituximab and azathioprine.

Case presentation: A 31-year-old male presented to the emergency department due to an episode of right arm weakness and left-sided facial weakness. Brain Magnetic Resonance Imaging (MRI) would show an ischemic change in the frontal and parietal lobes. A biopsy was done, which showed inflammatory infiltrates consistent with Primary Angiitis of the Central Nervous System. The patient was started on rituximab and showed improvement.

Clinical discussion: In this case, PACNS presented as episodic right arm weakness and left sided facial weakness. Gold standard for diagnosis is a biopsy from the inflamed region of the CNS that shows lymphocytic infiltration in a granulomatous pattern.

Conclusion: Despite its rarity, PACNS is a cause of morbidity if not caught and managed early. Therefore, considering PACNS in the differential diagnosis of a young patient with a history of frequent episodic neurological dysfunction is appropriate. Ischemic patterns on MRI further increase the index of suspicion around PACNS Confirmation of the diagnosis via biopsy from the inflamed region is the most accurate method.

1. Introduction

Primary Angiitis of the Central Nervous System (PACNS) is a rare form of vasculitis with an annual incidence rate of 2.4/1000000 [1]. PACNS is limited to the brain and the spinal cord. The pathological picture portrays inflammation and destruction of the central nervous system (CNS) vessels without evidence of vasculitis outside this level, making it a distinct clinical entity [1]. The leptomeningeal and parenchymal blood vessels are the main affected vessels in the disease process [2,3].

In general, CNS vasculitis can be primary or secondary. Various neurological insults can trigger CNS vasculitis, including infection, malignancy, radiation, cocaine ingestion and autoimmune diseases [3,4]. However, the precise pathogenesis remains obscure. However, the immune system appears to play a central role in the disease process [4]. Due to the lack of specific universal diagnostic criteria and imaging findings, the diagnosis remains a challenging one [1,2]. Presentation varies from a simple headache to focal weakness, encephalopathy and stroke-like presentations [2]. Central nervous system (CNS) imaging might include ischemic changes involving the subcortical white matter [3,4]. A definitive diagnosis is made by biopsy, which shows granulomatous inflammation [5,6]. Since the immune system is involved in the

* Corresponding author. Ramallah-Nablus Street, Ramallah, West Bank, Palestine.
E-mail addresses: Fajr.sarhan@students.alquds.edu (F.MA. Sarhan), ameer.abd1600a@comed.uobaghdad.edu.iq (A. Al-Jasim), ra.alaraj@gmail.com (R.SN. Alaraj), safwanfayyad56@gmail.com (S.FA. Abedalkhader), zaidghanim@gmail.com (Z. Ghanim).

https://doi.org/10.1016/j.amsu.2022.104040
Received 4 May 2022; Received in revised form 18 June 2022; Accepted 18 June 2022
Available online 23 June 2022

process, immunosuppressive agents are the cornerstones of treatment [4,5].

We hereby present a case and review of the literature on PACNS case presented in an episodic manner over a five-month duration. As a rare case, we emphasized the diagnostic challenge and limitations. We also explained the algorithm we took to reach the final diagnosis.

This paper has been reported in line with the CARE 2013 criteria [7].

2. Case presentation

A 31-year-old male patient presented to the emergency room complaining of right arm stiffness and left-sided facial weakness. Over the past five months, the patient reported similar episodes, also associated with headaches and slurred speech, from which he fully recovered. There was no vomiting, photophobia, fever or chills. However, there was a negative family history. Brain CT scans were done during his previous visits, and the results were unremarkable. During his second visit, the patient was prescribed carbamazepine as partial seizures accompanied by Todd's paralysis were suspected. However, his symptoms were still recurring during the period of carbamazepine treatment.

During this presentation, his Glasgow Coma Scale (GCS) was 15/15. Blood pressure was 138/85, Heart rate 76 beats per minute, respiratory rate was 15 breaths per minute, and the temperature was 37.1 Celsius orally. Examination reveals numbness, decreased sensation for light and crude touch, pain and temperature on the right side of the body. Motor examination revealed increased reflexes (+3) on the right and normal reflexes on the left side. Right-sided stiffness and a noticeable decrease in muscle power were noted on the same side. Examination of the face showed a left-sided facial weakness with an intact ability to close the eyelid and wrinkle the forehead bilaterally, indicating an upper motor facial nerve palsy.

Regarding imaging, a brain CT scan was done at the presentation and was insignificant. A decision for brain Magnetic Resonance Imaging (MRI) with contrast was made. MRI (Figs. 1A, B, C, D) showed ischemic changes in the parietal and frontal lobes. T2-FLAIR Imaging showed a low-grade lesion in the frontal and parietal lobes that required a biopsy to differentiate between inflammatory, demyelinating or tumoral etiologies. Cerebro-spinal fluid analysis was not done due to the fear of brain herniation, as the exact etiology was not yet identified. Carbamazepine therapy was stopped as the suspicion shifted from Todd's paralysis to intracranial pathology.

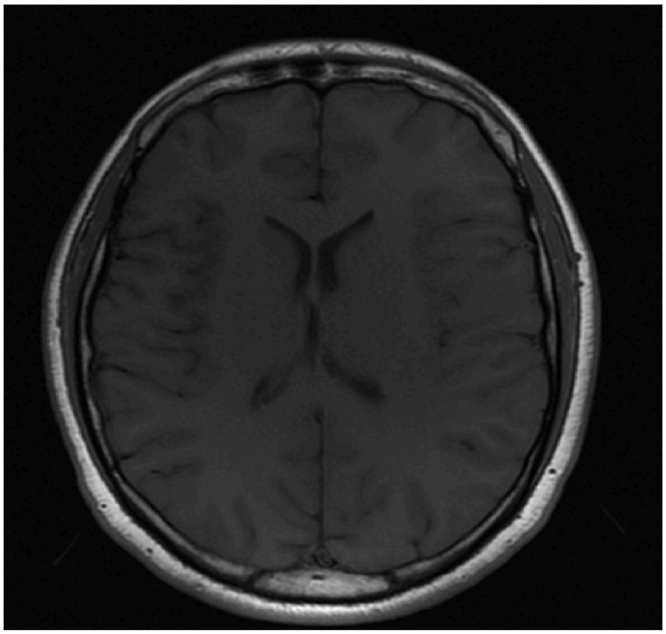

Fig. 1A. Axial T1 Sequence: no abnormalities.

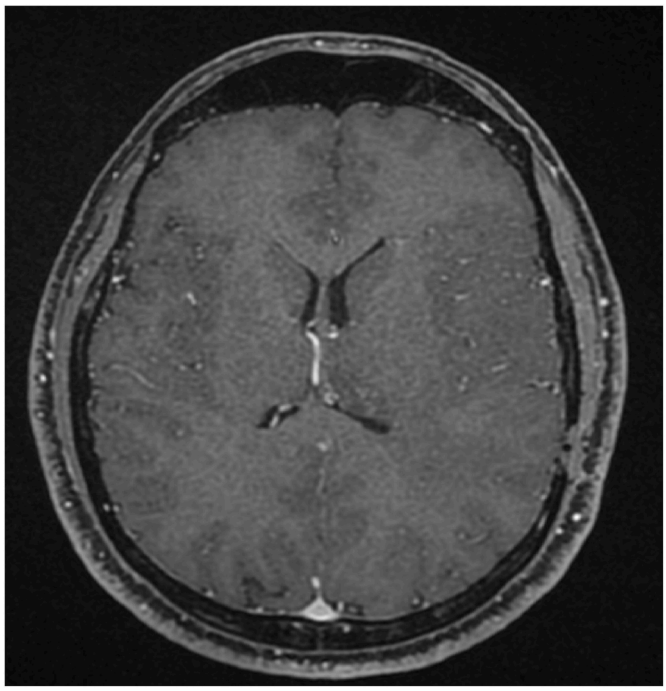

Fig. 1B. Axial T1 with Gadolinium Sequence: No enhancing lesions.

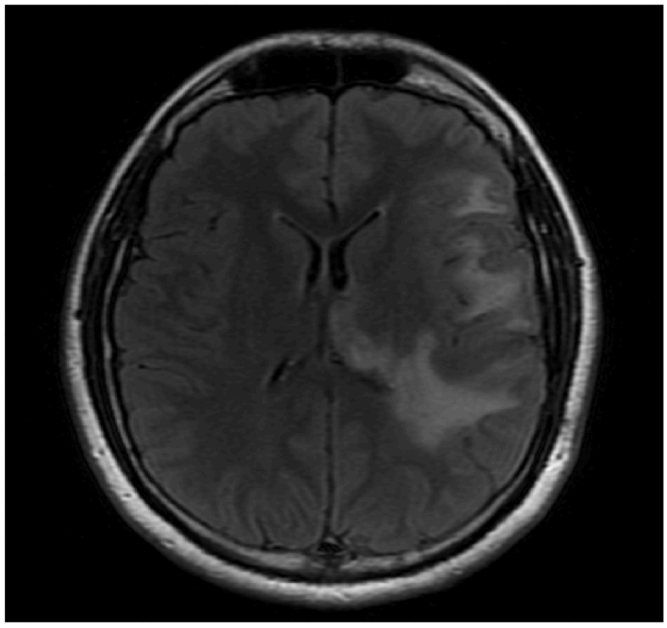

Fig. 1C. T2-FLAIR Sequence: Hyper-signal lesions in the cortical, subcortical, and basal ganglia of the left middle cerebral artery distribution.

A decision for a biopsy was made, and the patient was referred to the neurosurgical department. An intraoperative image of the brain is shown in Fig. 2A, which shows cerebral sinuses overlying a red congested and inflamed brain cortex. Biopsy results showed lymphocytic infiltration of the blood vessels consistent with cerebral angiitis in Fig. 2B. There were no other signs of vasculitis in the patient; thus, the patient was diagnosed with Primary Angiitis of the Central Nervous System.

The patient underwent testing for Hepatitis B, Hepatitis C, and PPD, which turned back with no significant findings. After that the patient

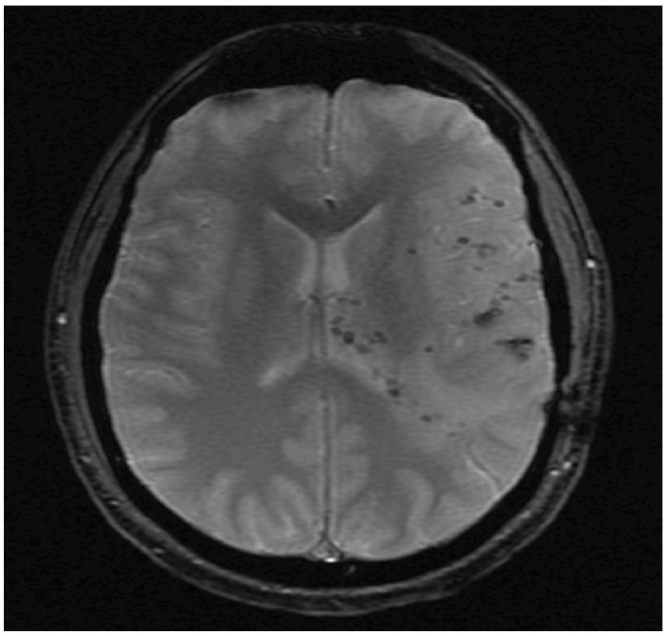

Fig. 1D. T2* Sequence: Patchy hypo-intensities in the cortical, subcortical, and basal ganglia of the left middle cerebral artery distribution.

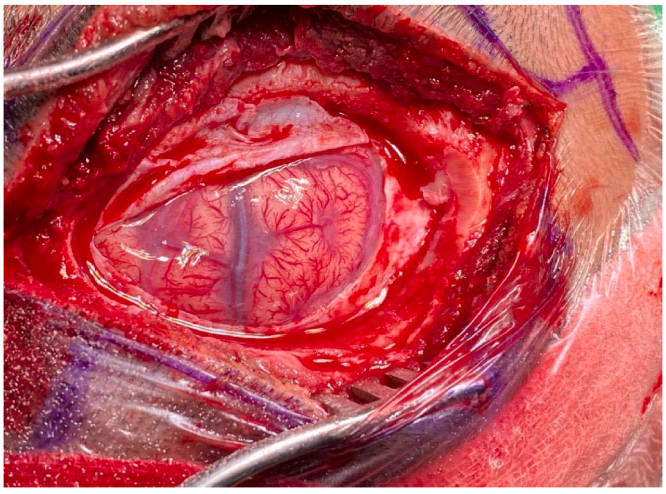

Fig. 2A. intraoperative imaging of the patient before the biopsy shows an inflamed cortex, increasing the suspicion of vasculitis.

was given two doses of rituximab 500mg IV two weeks apart. Rituximab 1 g was then administered once every 6 months. Over the following three months, the patient reported drastic improvement with his symptoms the patient didn't experience any further episodes. Currently the patient is following up to take his aforementioned treatment doses at the hospital where he was first diagnosed. No treatment adverse events were reported by the patient till this point.

3. Clinical discussion

Primary Angiitis of the Central Nervous System (PACNS) is a rare type of vasculitis that solely affects the Central Nervous System (CNS); PACNS has an annual incidence rate of 2.4/1000000. It is a multifactorial inflammatory process that primarily affects the arterioles and small-medium-sized CNS vessels, most likely located in the meninges and the cortex. The venous system is rarely affected [1].

PACNS diagnosis is challenging not only due to its rarity but also because of variable clinical presentation necessitating a high index of clinical suspicion and rigorous investigations to confirm the diagnosis and exclude mimics. Presenting symptoms vary widely between patients as it depends on the affected area in the brain. Classically, patients present with chronic symptoms due to the insidious onset of the inflammatory process. Acute cases present less commonly. Headache, Focal weakness, sensation loss, altered cognition and a stroke-like picture can be the presenting symptoms [2,3].This patient presented with episodic right-sided arm weakness and left-sided facial weakness.

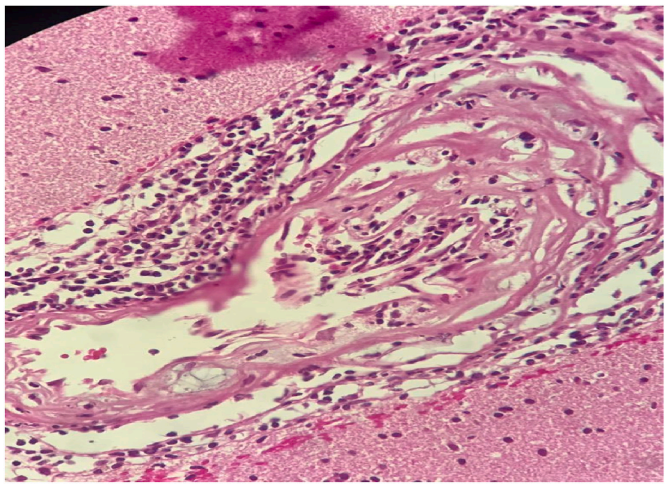

Fig. 2B. Histological image showing a lymphocytic infiltration of the blood vessels.

Radiological findings can be non-specific. The modality of choice for imaging diagnostics is Magnetic Resonance Imaging (MRI) [3]. It is worth mentioning that previous literature stated that a completely normal MRI essentially excludes the diagnosis if the CSF is also normal [3,4]. The most common findings are located in the subcortical white matter, followed by the deep gray matter [4]. Infarcts are commonly seen in up to 50% of cases, which are usually multiple and bilateral. Shiner EA and coworkers stated that PACNS could also present as tumor-like mass lesions [3]. One-third of the affected cases showed Gadolinium enhancement. In our case, the MRI (Figs. 1A, B, C, D) showed no enhancing lesions on the Axial T1 or the Axial T1 with Gadolinium enhancement. FLAIR T2 showed hyper-intense lesions in the temporal and parietal lobes. A magnetic Resonance Angiogram (MRA) will typically show beading patterns with alternating areas of stenosis. Small vessel vasculitis may not show this finding. The limitations of the MRA caused a debate about its use as the gold standard diagnostic modality. It is not highly sensitive to detecting vessel changes. It has low specificity, as a vast range of non-inflammatory processes can mimic the disease presentation on the MRA, including atherosclerosis, radiation vasculopathy, fibromuscular dysplasia, and Reversible Vasoconstriction Syndrome [5,6].

Cerebrospinal fluid (CSF) abnormalities are seen in 80–90% of cases. CSF analysis will typically show a non-specific increase in the total protein and white blood cells count that will not exceed 250 cells/uL. Acute phase reactants such as ESR and CRP will be elevated [8]. CSF analysis was not done in our case due to the fear of brain herniation.

Previous literature showed that a normal MRI and no CSF findings could provide a substantial negative predictive value to exclude PACNS [8].

Currently, the Gold standard for the diagnosis is a biopsy [6]. Therefore, it is encouraged to be done to all suspected cases of the PACNS. Biopsy excludes other potential differential diagnoses such as Infections, abscesses, primary CNS lymphoma and lymphomatoid granulomatosis. The probability of a false-negative biopsy is high due to its segmental nature of inflammation. False-negative biopsies have been

reported due to the sampling error [6,9]. For optimal yield, Lie JT in his literature review, stated that the biopsy should be taken from the non-dominant temporal tip [9]. Leptomeninges should be biopsied as well due to their frequent involvement. The classical picture on histology will show lymphocytic infiltrates in a granulomatous inflammatory pattern with multinucleated giant cells. Other findings of plasma cells, Langerhans cells and histiocytes have been noted [9].

In some cases, amyloid deposition may be found [10,11]. In our case, biopsies were taken, and histological analysis showed inflammatory infiltrates in a granulomatous pattern consistent with PACNS diagnosis. The major limitation of the biopsy was the need for craniotomy, which has all the adverse effects of open surgery, especially general anesthesia-related adverse effects.

Treatment recommendations for PACNS are mainly based on retrospective studies, and expert opinions as the prospective and randomized treatment trials that show the evidence-based strategies for managing PACNS are lacking so far [12,13]. Hence, current therapeutic regimes are adopted from those validated in systemic vasculitis on the ground of pathological concordance [13]. There are three treatment approaches for PACNS: corticosteroids, immunosuppressant and biologicals [13]. Immune suppressive therapy was found to be the cornerstone for halting the disease progression [12]. Treatment is divided into induction and maintenance phases [13]; cyclophosphamide and methylprednisolone are currently used for induction therapy; this combination is equally effective with methylprednisolone therapy alone but is associated with fewer relapses [13,14]. A Multicenter cohort study showed that most of the patients treated with combination therapy had a significant reduction in morbidity. This study suggests that an early diagnosis and aggressive treatment might improve outcomes. Therefore, in patients with a severe and rapidly progressive disease course, treatment-refractory disease or relapses, a combination with an immunosuppressant should strictly be considered [13]. Rituximab is an effective treatment for refractory PACNS [15]. Gastric ulcer and venous thrombosis prophylactic medications are to be implemented in the treatment plan [13]. Positive data supports the use of biological agents (rituximab and tumor necrosis factor-alpha blockers) with an equal ability to induce remission in PACNS patients compared to glucocorticoids and immunosuppressant [13–15]. Thus, patients not tolerating steroids and immunosuppressant can be started on rituximab or tumor necrosis factor-alpha inhibitors [13]. Our patient was started on rituximab 500mg, and a similar dose was given after two weeks as an induction phase. The patient will be on 1 g of rituximab once every six months.

Whilst induction treatment aims to achieve remission and avoid bad outcomes; maintenance treatment aims to prevent future relapses and long-term disabilities [13]. PACNS maintenance therapy typically starts 4–6months after initiation of induction therapy, and disease-modifying drugs such as methotrexate, mycophenolate mofetil, and azathioprine are the ones involved in this treatment plan [13,14]. Factors influencing therapeutic decisions include comorbidities, clinician preference and side effects. A cohort study involving fourteen children with PACNS showed that treatment with mycophenolate mofetil for maintenance therapy led to fewer adverse events than azathioprine. Commonly associated adverse effects with azathioprine are elevated liver enzymes [14,15]. During the maintenance therapy, vitamin D and calcium are required to prevent adverse effects like osteoporosis. Pneumocystis pneumonia and gastric ulcer prophylaxis are also required [14,16].

Treatment duration, costs, access to medications, and the immunosuppressive nature of the medications, especially at the peak of the COVID-19 pandemic, raised concern for our team regarding the continuity of treatment for the patient.

4. Conclusion and take-home messages

Despite its rarity, PACNS is a cause of morbidity if not caught and managed early. Therefore, considering PACNS in the differential diagnosis of a young patient with a history of frequent episodic neurological dysfunction is appropriate. Ischemic patterns on MRI further increase the index of suspicion around PACNS Confirmation of the diagnosis via biopsy from the inflamed region is the most accurate method.

Ethical approval

This study is exempt from ethical approval in our institution.

Sources of funding

The authors declare that writing and publishing this manuscript was not funded by any organization.

Author contribution

Data collection: Fajr M A Sarhan, Safwan F A Abedalkhader.

Writing the manuscript: Fajr M A Sarhan, Ameer Al-Jasim, Safwan F A Abedalkhader, Zaid Ghanim, Rami S. N. Alaraj.

Imaging description: Zaid Ghanim, Rami S. N. Alaraj, Fajr M A Sarhan, Safwan F A Abedalkhader.

Reviewing & editing the manuscript: Fajr M A Sarhan, Rami S. N. Alaraj, Ameer Al-Jasim.

Grammar and Syntax check: Rami S. N. Alaraj.

Consent

Written informed consent was obtained from the patient for Publication of this case report and accompanying images. A copy of the informed consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

- Name of the registry: N/A.
- Unique Identifying number or registration ID: N/A
- Hyperlink to your specific registration (must be publicly accessible and will be checked): N/A

Guarantor

Zaid Ghanim, M.D. Al-Quds University, Ramallah-West Bank, Palestine, state of.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

[1] S.A. Paul, D. Roy, G.P. Mondal, R. Bhattacharyya, K.C. Ghosh, S. Das, H. Krishna, C. Patra, J. Kiran, J. Benito-León, Primary angiitis of the central nervous system–A challenging diagnosis, J. Neuroimmunol. 366 (2022 May 15), 577844.

[2] C. Salvarani, R.D. Brown Jr., G.G. Hunder, Adult primary central nervous system vasculitis, Lancet 380 (9843) (2012 Aug 25) 767–777, https://doi.org/10.1016/S0140-6736(12)60069-5. Epub 2012 May 9. PMID: 22575778.

[3] E.A. Shiner, A.S. Zagami, An Illustrative Case of Primary Angiitis of the Central Nervous System, vol. 2, SAGE Open Med Case Rep, 2014, https://doi.org/10.1177/2050313X14559638, 2050313X14559638. Published 2014 Nov 14.

[4] E.M. Arsava, E. Yilmaz, M.A. Topcuoglu, Incidental DWI lesions in patients with recent small subcortical infarctions, J. Stroke Cerebrovasc. Dis. 31 (4) (2022 Apr 1), 106304.

[5] A. Ishizu, T. Kawakami, H. Kanno, K. Takahashi, T. Miyazaki, E. Ikeda, T. Oharaseki, Y. Ogawa, M. Onimaru, M. Kurata, D. Nakazawa, Expert perspectives on pathological findings in vasculitis, Mod. Rheumatol. (2022 May 10).
[6] G. Uçar, E. Dandıl, Automatic detection of white matter hyperintensities via mask region-based convolutional neural networks using magnetic resonance images, in: Deep Learning for Medical Applications with Unique Data 1, 2022 Jan, pp. 153–179 (Academic Press).
[7] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus surgical CAse REport (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230.
[8] T. Ruland, J. Wolbert, M.G. Gottschalk, et al., Cerebrospinal fluid concentrations of neuronal proteins are reduced in primary angiitis of the central nervous system, Front. Neurol. 9 (2018) 407, https://doi.org/10.3389/fneur.2018.00407. Published 2018 Jun 5.
[9] A. Corovic, S. Kelly, H.S. Markus, Cerebral amyloid angiopathy associated with inflammation: a systematic review of clinical and imaging features and outcome, Int. J. Stroke 13 (3) (2018 Apr) 257–267.
[10] Nicolás Coronel-Restrepo, Fabio Bonilla-Abadía, Omar A. Cortes, Jorge H. Izquierdo, Alberto M. Shinchi, Juan C. Bravo, Gabriel J. Tobón, Carlos A. Cañas, Primary angiitis of the central nervous system: a report of three cases from a single Colombian center, Case Rep. Neurol. Med. (2013), https://doi.org/10.1155/2013/940438, 2013, Article ID 940438, 4 pages.
[11] Bernstein J E, Podkovik S, Kashyap S, et al. (June 08, 2020) primary angiitis of the central nervous system presenting as a cerebral mass lesion: a case report and literature review. Cureus 12(6): e8511. doi:10.7759/cureus.8511.
[12] S. Wang, I. Breskovska, S. Gandhy, A.R. Punga, J.T. Guptill, H.J. Kaminski, Advances in autoimmune myasthenia gravis management, Expert Rev. Neurother. 18 (7) (2018 Jul 3) 573–588.
[13] C. Beuker, A. Schmidt, D. Strunk, P.B. Sporns, H. Wiendl, S.G. Meuth, J. Minnerup, Primary angiitis of the central nervous system: diagnosis and treatment, Ther. Adv. Neurol. Disord. 11 (2018), 1756286418785071, https://doi.org/10.1177/1756286418785071.
[14] C. Salvarani, R.D. Brown, T.J. Christianson, et al., Adult primary central nervous system vasculitis treatment and course: analysis of one hundred sixty-three patients, Arthritis Rheum. 67 (2015) 1637–1645.
[15] N.K. Paramasivan, S. Sundaram, D.P. Sharma, S.E. Sreedharan, P.N. Sylaja, Rituximab for refractory primary angiitis of the central nervous system: experience in two patients, Mult. Scler. Relat. Disord. 51 (2021 Jun), 102907, https://doi.org/10.1016/j.msard.2021.102907. Epub 2021 Mar 18. PMID: 33773272.
[16] M.A. Alba, G. Espígol-Frigolé, S. Prieto-González, et al., Central nervous system vasculitis: still more questions than answers, Curr. Neuropharmacol. 9 (3) (2011) 437–448, https://doi.org/10.2174/157015911796557920.