Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6560-20
Intern Med 60: 2321-2326, 2021
http://internmed.jp

【 CASE REPORT 】

Reversible Cerebral Vasoconstriction Syndrome without Headache That Was Initially Suspected of Being Primary Angiitis of the Central Nervous System

Taiki Matsubayashi, Ayako Oniki, Misako Furuki and Masato Obayashi

Abstract:
A 48-year-old man had convulsions, and magnetic resonance angiography (MRA) showed diffuse constriction of the cerebral arteries. He was suspected of having primary angiitis of the central nervous system (PACNS) and treated with steroid for three days. The MRA abnormality disappeared after a week. After 69 days, he developed dizziness, and MRA revealed recurrence of cerebral artery stenosis. Nevertheless, the symptoms and abnormal MRA findings recovered promptly without treatment. He was diagnosed with reversible cerebral vasoconstriction syndrome (RCVS) without headache. This case suggests that RCVS should be a differential diagnosis in patients without headache whose MRA findings show multiple cerebral artery stenosis.

Key words: reversible cerebral vasoconstriction syndrome, headache, primary angiitis of the central nervous system, magnetic resonance angiography

(Intern Med 60: 2321-2326, 2021)
(DOI: 10.2169/internalmedicine.6560-20)

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a clinical and radiologic syndrome characterized by a severe headache and multifocal segmental vasoconstriction of cerebral arteries that improves spontaneously within three months (1). A wide variety of brain lesions, such as convexity subarachnoid hemorrhaging (cSAH), intracerebral hemorrhaging (ICH), posterior reversible encephalopathy syndrome (PRES), and ischemic stroke (IS), are known to be complicated by RCVS (2). The characteristic headache is a thunderclap headache (TCH) that is hyperacute severe and reaches its maximal intensity in less than a minute (3). TCH is the most common symptom of RCVS, and 78-100% of patients experience TCH as initial manifestation (4-6). Thus, RCVS is typically diagnosed on the basis of the clinical and radiologic presentation by excluding other causes of TCH (7). In contrast, Wolff et al. reported that some patients with RCVS do not have TCH, and a few of them do not have any headache at all (8).

We herein report a patient with RCVS without headache over the course of two attacks whose symptoms were difficult to differentiate from those of primary angiitis of the central nervous system (PACNS).

Case Report

A 48-year-old man was transferred to our hospital due to a convulsion. In the morning of the day when he had the convulsion, he had conversed with his family in a normal healthy state. He was undergoing treatment for psoriasis vulgaris with apremilast and had a history of untreated hypertension.

When arriving at our hospital, his consciousness level was disturbed (Glasgow Coma Scale 4-4-5), and he was vomiting. Therefore, he was unable to follow the instructions of the medical staff. His blood pressure was 169/101 mmHg, pulse was 129 beats per minute, body temperature was 36.1°C, respiratory rate was 36 breaths per minute, and oxygen saturation was 100% (10 L/min reservoir mask). He had red scaly rashes on his limbs and trunk. His pupils were

Department of Neurology, National Hospital Organization Disaster Medical Center, Japan
Received: October 21, 2020; Accepted: January 5, 2021; Advance Publication by J-STAGE: February 22, 2021
Correspondence to Dr. Masato Obayashi, oobayashi.masato.zm@mail.hosp.go.jp

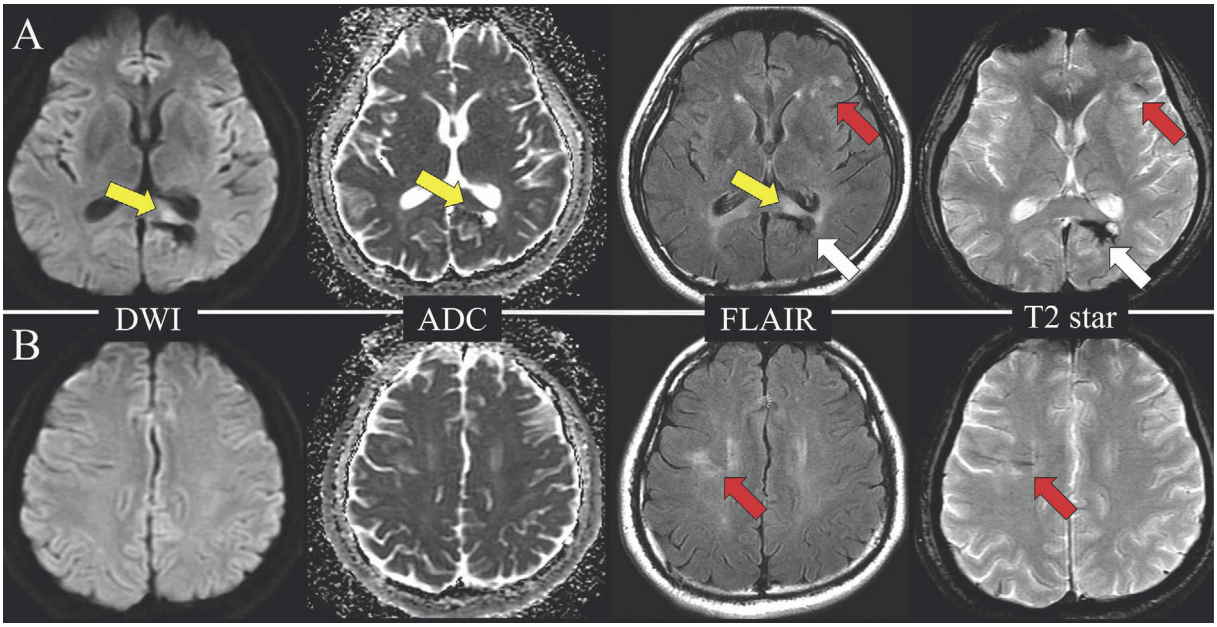

Figure 1. Head MRI findings on admission. Upper (A) and lower panels (B) show axial slices at the level of the foramen of Monro and centrum semiovale, respectively. (A) Diffusion-weighted imaging (DWI) demonstrates a high signal intensity in the left deep white matter near the splenium of the corpus callosum; without changes in the apparent diffusion coefficient (ADC). Fluid-attenuated inversion recovery (FLAIR) MRI shows a high signal intensity in the same area, suggesting subacute phase or later cerebral infarction (yellow arrows). FLAIR MRI also shows a low intensity area near the cerebral infarction with a low intensity on T2 star-weighted imaging, indicating old hemorrhage (white arrows). (A, B) FLAIR MRI shows multiple high intensity areas in the left frontal lobe and right deep white matter with or without low intensity on T2 star-weighted imaging, indicating old infarction or hemorrhage, respectively (red arrows).

equal in size (3.0 mm in diameter), round, and reactive to light. Although it was difficult to evaluate his strength accurately due to disturbance of consciousness, there was no obvious motor paralysis. The deep tendon reflexes of all four limbs were decreased. He showed no meningeal signs, such as nuchal rigidity, Kernig's sign and Brudzinski's sign. Other physical and neurological examinations were normal.

On laboratory tests, his white blood cell (WBC) count was 20,000/μL with 89.3% neutrophils. Both D-dimer (<0.5 μg/mL) and C-reactive protein (<0.05 mg/dL) levels were within the normal ranges. Immunological tests for rheumatoid factor, antinuclear antibodies, anti SS-A/SS-B antibodies, anti-neutrophil cytoplasmic antibody, anti-cardiolipin antibody, and lupus anticoagulant were negative. A cerebrospinal fluid (CSF) examination showed increased WBC counts (76/3 μL) with 99% lymphocytes, and normal ranges of protein (44 mg/dL), glucose (66 mg/dL), and IgG index (0.58). The CSF culture and herpes simplex virus (HSV)-1/2DNA test were negative.

Whole-body computed tomography (CT) with contrast revealed that there were no organs and blood vessels with poor contrast enhancement. Diffusion-weighted magnetic resonance imaging (MRI) of the head without contrast demonstrated a high signal intensity in the left deep white matter near the splenium of the corpus callosum, without a change in the apparent diffusion coefficient (ADC). Fluid-attenuated inversion recovery (FLAIR) MRI showed a high signal intensity in the same area. The lesion was suspected to be a subacute phase or later cerebral infarction (Fig. 1A). FLAIR MRI showed a low-intensity area near the cerebral infarction with a low intensity on T2 star-weighted imaging, indicating old hemorrhaging (Fig. 1A). FLAIR MRI also revealed multiple high-intensity areas in the left frontal lobe and right deep white matter with or without low intensity on T2 star-weighted imaging, indicating old infarction or hemorrhaging, respectively (Fig. 1A, B). MRA revealed multifocal segmental cerebral artery vasoconstriction, which was most prominent in the bilateral posterior cerebral arteries (Fig. 2A).

After arriving, he was intubated to secure the airway. Midazolam and propofol were used for sedation and to prevent convulsions. Levetiracetam and valproic acid were initiated for convulsion. Because he was suspected of PACNS based on the results of the MRA and CSF analysis, high-dose intravenous methylprednisolone (1,000 mg daily for 3 days) was initiated from the next day of hospitalization. Intravenous acyclovir (10 mg/kg Q8h) was administered until the result of HSV-DNA was confirmed to be negative. Paroxysmal waves were not detected on the electroencephalogram two days after administration. A follow-up CSF examination on day 8 showed normalized WBC counts (2/3 μL). The patient did not develop convulsions after hospitalization, so he

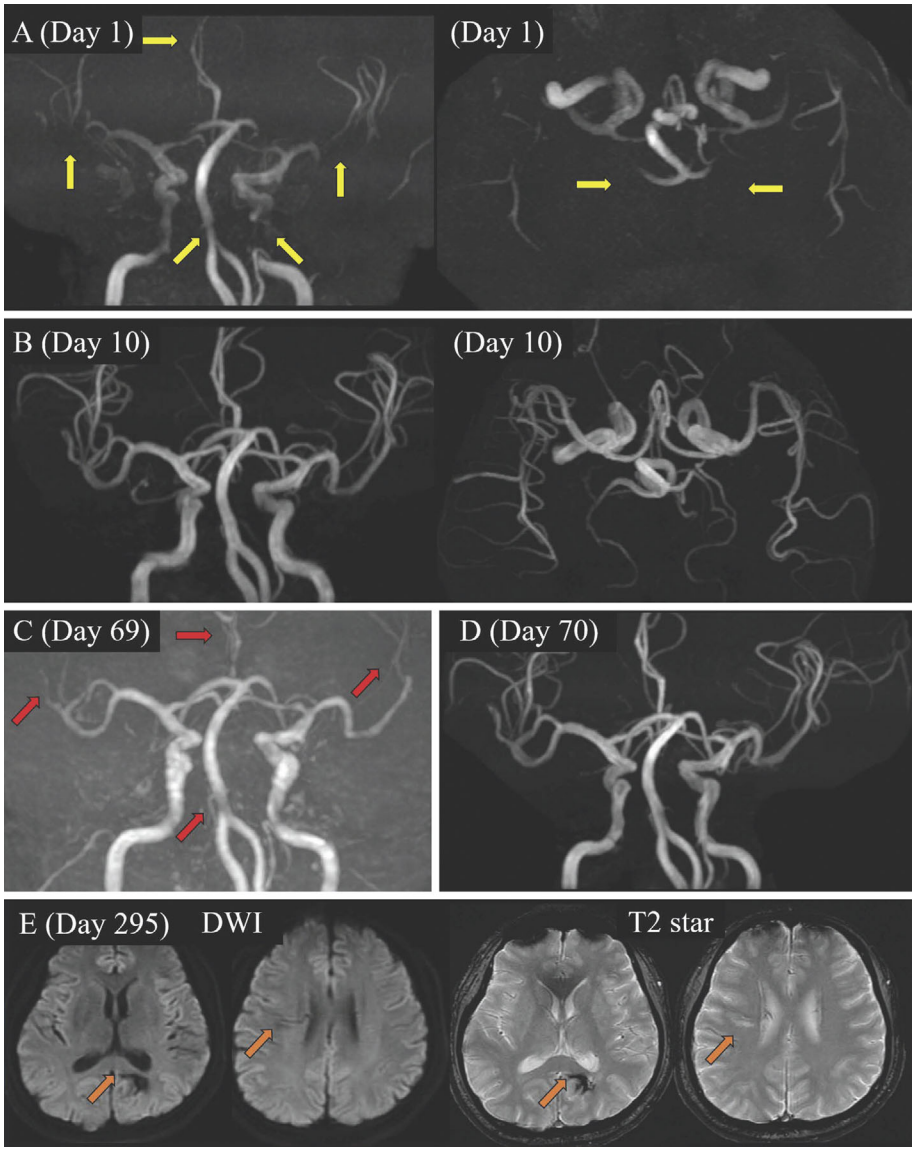

Figure 2. **Time course of the MRA and MRI findings 1 (A), 10 (B), 69 (C), 70 (D), and 295 days (E) after onset. (A) Multifocal segmental cerebral artery vasoconstriction is most prominent in the bilateral posterior cerebral arteries (yellow arrows). (B) Disappearance of the abnormal findings observed on day 1. (C) Multiple cerebral artery stenosis (red arrows). (D) Normalization of cerebral artery stenosis. (E) No new lesions were detected (orange arrows).**

was extubated. Follow-up MRA showed that the multifocal segmental cerebral artery vasoconstriction had disappeared (Fig. 2B). There were no neurological abnormalities, and he was discharged on day 26. On day 52, amlodipine was initiated for hypertension.

On day 69, he developed dizziness and consulted another hospital. MRA showed multiple cerebral artery stenosis (Fig. 2C), and he was transferred to our hospital on day 70. On arrival, MRI and CSF examinations were performed. MRI and MRA revealed no new intracranial lesions and cerebral artery stenosis, respectively (Fig. 2D). His CSF contained WBCs (1/3 μL) and protein (34.2 mg/dL) concentrations within the normal range. In addition, a neurological examination revealed no evidence of abnormal findings, and the dizziness had disappeared at arrival. The patient also reported that there was no headache during the course of the two clinical attacks. Finally, these findings led us to exclude PACNS, and he was diagnosed with RCVS without headache. No new lesions were detected on follow up MRI after hospital discharge on day 295 (Fig. 2E).

Discussion

The exact pathogenesis of headache in RCVS remains unclear (9); however, it is inferred that a sudden change in central vascular tone may stretch the vessel walls and result in TCH at the initial stage of RCVS (3). As with TCH, seizures are an early complication of RCVS, and are present in 1-17% of cases (1). Thus, the presence of headache in RCVS cases with seizure may be unclear, as patients with disturbed consciousness cannot describe their symptoms (10, 11). Although the possibility that our patient had

Table. The Characteristics of Patients without Headache Associated with RCVS.

Case	Age (y)	Sex	Precipitant factor	Neurological symptoms	Complications	Outcome	Reference
1	25	Female	None	Diplopia, right ataxia	IS	mRS 0	12
2	35	Male	None	Left hemiparesis	IS	mRS 0	12
3	27	Male	Cannabis	Right paresthesia	IS	mRS 0	12
4	38	Male	Nasal decongestants	Right ataxia, dysarthria	IS	mRS 1	12
5	36	Male	None	Vertigo, right hemiparesis	IS	mRS 0	12
6	31	Female	Postpartum Serotonergic antidepressant	Left hemiparesis	IS	Persistent deficit	13
7	24	Female	Postpartum	Generalized tonic-clonic seizure	cSAH	Asymptomatic	14
8	42	Male	Cannabis	Transient episodes of right hemiparesis	IS	Asymptomatic	15
9	32	Female	Pregnancy	Dizziness, diplopia	IS	mRS 0	16
10	46	Male	None	Visual field defect, left lower limb weakness	IS	NA	17
11	48	Male	None	First attack; None Second attack; convulsion Third attack; dizziness	IS, ICH	mRS 0	Our case

RCVS: reversible cerebral vasoconstriction syndrome, IS: ischemic stroke, cSAH: convexity subarachnoid hemorrhage, mRS: modified Rankin Scale, NA: not attributable, ICH: intracerebral hematoma

headache at the first hospitalization cannot be ruled out, he insisted that there was no headache during both the first hospitalization before the convulsion and the second hospitalization. Previous reports have presented detailed information of the clinical and radiological features of 10 patients with RCVS without headache (Table) (12-17). These reports showed several characteristics of RCVS without headache. First, all of the patients had cerebrovascular disease accompanied by RCVS; nine had ischemic stroke, and one had cSAH. In the present case, MRI showed subacute or later phase cerebral infarction and old hemorrhaging. These may have been complications of RCVS, as cerebrovascular disease is often associated with RCVS. Nonetheless, he did not have any symptoms before the day of the hospitalization. We concluded that RCVS did not accompany ischemic stroke at the time when he was hospitalized with the convulsion. This case suggests that RCVS can lead to asymptomatic attack, and it is rare for clinical RCVS attack without headache and cerebrovascular disease to occur together. Regarding the patient's dizziness, stenosis of the basilar artery seemed to result in the symptoms of a transient ischemic attack. Second, the clinical outcomes of almost all previously described patients were good, and all were under 50 years old. Our patient had common features with those patients in that no sequelae remained, and he was 48 years old.

The diagnostic criteria for RCVS proposed by Calabrese in 2007 include the presence of severe acute headache (18). Clinically, RCVS is considered in patients with a hyperacute severe headache (18), whereas radiological aspects are important in cases of RCVS without headache (8). Multiple cerebral artery stenosis is a critical feature of RCVS. Many diseases, such as PACNS, secondary central nervous system vasculitis, infectious disease, multiple embolic cerebral infarcts, anti-phospholipid antibody syndrome, and Moyamoya disease, have the same feature (19). In our case, examinations such as laboratory tests, whole-body CT, and head MRI excluded differential diagnoses other than PACNS.

We initially suspected that PACNS was the cause of his symptoms based on the results of MRA and CSF studies. The classical diagnostic criteria for PACNS proposed by Calabrese and Mallek in 1988 include angiographic and histopathological examinations (20). As with digital subtraction angiography (DSA), MRA can also detect multilocular stenosis, multiple narrowing and dilatation, and other abnormal findings of intracranial vessels that are caused by central nervous system vasculitis (21) and can be implemented in the PACNS diagnostic approach (22). Nevertheless, the limited diagnostic specificity of MRA and DSA leads to difficulty distinguishing between PACNS and RCVS (23). Thus, Beuker et al. proposed considering a CSF profile for the PACNS diagnosis (24). In PACNS, the CSF analysis findings are abnormal (leucocytosis and high total protein concentrations); however, in RCVS, these findings are normal or near normal (protein concentrations <100 mg/dL, <15 WBC/μL) (18). In our case, PACNS was suspected rather than RCVS initially because the patient's MRA showed multifocal vessel narrowing, and his CSF study showed leucocytosis. DSA was not performed for two reasons. First, we had already detected abnormal MRA findings that were compatible with the diagnosis of PACNS. Second, DSA reportedly sometimes aggravates ischemic lesions of PACNS (25) and vasoconstriction of RCVS (2). In addition, we did not perform a biopsy before initiating corticosteroid therapy because it is highly invasive; however, a biopsy is crucial for a PACNS diagnosis (26). A biopsy is encouraged, especially when considering prolonged immunosuppressant

treatment of patients suspected of PACNS (23).

In addition to CSF analyses, it has been reported that the characteristic headache can help distinguish RCVS from PACNS (24); this is also referenced in the diagnostic criteria of RCVS (18). TCHs are typical in RCVS, whereas they are subacute and progressive in PACNS. However, the headache characteristic is not useful when patients do not have headaches. Of note, a CSF analysis of convulsion and cerebral infarcts may show pleocytosis, as seen in our case (27, 28). It is thus challenging to differentiate RCVS without headache and PACNS at first consultation, and we may need to initiate corticosteroid therapy because early treatment is indispensable to avoid poor outcomes in PACNS (29). The cerebrovascular abnormality observed in our case normalized completely and rapidly, while that of PACNS is frequently irreversible (30). Thus, our case was correctly diagnosed thanks to careful follow-up.

In conclusion, we experienced a patient with RCVS who presented with convulsion and dizziness. RCVS should be considered as a differential diagnosis for patients without headache whose MRA show multifocal segmental cerebral artery vasoconstriction. At the initial consultation, it is difficult to distinguish RCVS without headache from PACNS. The clinical course after the onset may play a key role in the diagnosis, and a biopsy should be considered according to the clinical course.

The authors state that they have no Conflict of Interest (COI).

References

1. Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol **11**: 906-917, 2012.
2. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain **130**: 3091-3101, 2007.
3. Chen SP, Fuh JL, Wang SJ. Reversible cerebral vasoconstriction syndrome: current and future perspectives. Expert Rev Neurother **11**: 1265-1276, 2011.
4. Chen SP, Fuh JL, Wang SJ, et al. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. Ann Neurol **67**: 648-656, 2010.
5. Ducros A, Fiedler U, Porcher R, Boukobza M, Stapf C, Bousser MG. Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. Stroke **41**: 2505-2511, 2010.
6. Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. Arch Neurol **68**: 1005-1012, 2011.
7. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd ed (beta version). Cephalalgia **33**: 629-808, 2013.
8. Wolff V, Ducros A. Reversible cerebral vasoconstriction syndrome without typical thunderclap headache. Headache **56**: 674-687, 2016.
9. Miller TR, Shivashankar R, Mossa-Basha M, Gandhi D. Reversible cerebral vasoconstriction syndrome, Part 1: epidemiology, pathogenesis, and clinical course. AJNR Am J Neuroradiol **36**: 1392-1399, 2015.
10. Fugate JE, Wijdicks EF, Parisi JE, et al. Fulminant postpartum cerebral vasoconstriction syndrome. Arch Neurol **69**: 111-117, 2012.
11. Marder CP, Donohue MM, Weinstein JR, Fink KR. Multimodal imaging of reversible cerebral vasoconstriction syndrome: a series of 6 cases. AJNR Am J Neuroradiol **33**: 1403-1410, 2012.
12. Wolff V, Armspach JP, Lauer V, et al. Ischaemic strokes with reversible vasoconstriction and without thunderclap headache: a variant of the reversible cerebral vasoconstriction syndrome? Cerebrovasc Dis **39**: 31-38, 2015.
13. Fugate JE, Ameriso SF, Ortiz G, et al. Variable presentations of postpartum angiopathy. Stroke **43**: 670-676, 2012.
14. Spitzer C, Mull M, Rohde V, Kosinski CM. Non-traumatic cortical subarachnoid haemorrhage: diagnostic work-up and aetiological background. Neuroradiology **47**: 525-531, 2005.
15. Tsivgoulis G, Lachanis S, Papathanasiou MA, Chondrogianni M, Brountzos EN, Voumvourakis K. Cannabis-associated angiopathy: an uncommon cause of crescendo transient ischemic attacks. Circulation **130**: 2069-2070, 2014.
16. Kasuya C, Suzuki M, Koda Y, et al. A headache-free reversible cerebral vasoconstriction syndrome (RCVS) with symptomatic brain stem ischemia at late pregnancy as a rare manifestation of RCVS resolved with termination of pregnancy by semi-urgent cesarean section. Oxf Med Case Reports **2018**: omy101, 2018.
17. Kim BS, Park YK, Sunwoo MK, Yu HJ, Jeong EH, Kim DY. Is the presence of headache indispensable in diagnosing reversible cerebral vasoconstriction syndrome? J Clin Neurol **15**: 588-590, 2019.
18. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med **146**: 34-44, 2007.
19. Hajj-Ali RA, Calabrese LH. Diagnosis and classification of central nervous system vasculitis. J Autoimmun **48-49**: 149-152, 2014.
20. Calabrese LH, Mallek JA. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore) **67**: 20-39, 1988.
21. Eleftheriou D, Cox T, Saunders D, Klein NJ, Brogan PA, Ganesan V. Investigation of childhood central nervous system vasculitis: magnetic resonance angiography versus catheter cerebral angiography. Dev Med Child Neurol **52**: 863-867, 2010.
22. Berlit P, Kraemer M. Cerebral vasculitis in adults: what are the steps in order to establish the diagnosis? Red flags and pitfalls. Clin Exp Immunol **175**: 419-424, 2014.
23. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. Arch Neurol **66**: 704-709, 2009.
24. Beuker C, Schmidt A, Strunk D, et al. Primary angiitis of the central nervous system: diagnosis and treatment. Ther Adv Neurol Disord **11**: 1756286418785071, 2018.
25. Krings T, Willmes K, Becker R, et al. Silent microemboli related to diagnostic cerebral angiography: a matter of operator's experience and patient's disease. Neuroradiology **48**: 387-393, 2006.
26. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. Lancet Neurol **10**: 561-572, 2011.
27. Susse M, Saathoff N, Hannich M, von Podewils F. Cerebrospinal fluid changes following epileptic seizures unrelated to inflammation. Eur J Neurol **26**: 1006-1012, 2019.
28. De Reuck J, De Coster W, Vander Eecken H. Cerebrospinal fluid cytology in acute ischaemic stroke. Acta Neurol Belg **85**: 133-136, 1985.
29. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol **62**: 442-451, 2007.
30. Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. Isr Med Assoc J **19**: 448-453, 2017.