1.1 Isolated Vasculitis of the Central Nervous System

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Case Presentation

A 53-year-old female was admitted to the emergency department with complaints of sudden facial paralysis and impaired speech. The patient's temperature was 36.7 °C, heart rate, 79 beats/min, blood pressure, 100/65 mm Hg and respiratory rate, 21 breaths/min with oxygen saturation of 99% on room air. Physical examination revealed no abnormalities in the head, neck, chest, abdomen or lymph nodes. On neurological exam, she demonstrated slightly decreased motor strength in her left side predominantly upper extremity. Fundoscopic examination was normal. Her medical and family history was unremarkable. No history of drug abuse or hormonal therapy was reported. Laboratory studies, including total peripheral blood count, biochemical screen, Fe, ferritin, HbA1c, vitamin B12, folic acid, thyroid function, and renal and hepatic functions, were normal. The erythrocyte sedimentation rate and C-reactive protein were slightly elevated. Inflammatory and coagulopathy panel antinuclear antibody, rheumatoid factor, antineutrophilic cytoplasmic autoantibody, HLAB27, serum angiotensin-converting enzyme (ACE), lupus anticoagulant, antithrombin, protein S, protein C, factor VIII levels, homocysteine levels, antiphospholipid antibodies, factor V Leiden mutation and activated protein C resistance were negative. Results of protein electrophoresis were within normal limits.

Diffusion magnetic resonance imaging (MRI) of the patient revealed an acute ischemic focus in the right basal ganglia and anterior limb of right internal capsule. Critical right middle cerebral artery stenosis was detected in MR angiography and CT angiography. The patient was hospitalized for further evaluation (Figure 1.1.1).

No pathological findings were detected in transthoracic echocardiography and 24-hour rhythm Holter, and transesophageal echocardiography reported a tunnel-type patent foramen ovale that did not show spontaneous passage.

Cerebrospinal fluid (CSF) analysis was normal except for slightly increased protein content and mild lymphocyctic leukocytosis.

The patient's complaints completely resolved spontaneously within a week. Digital subtraction angiography revealed an occlusion in the right anterior cerebral artery A1 segment and a 50% stenosis in the right middle cerebral artery M1 segment. In vessel-wall MRI (VWI MR) to examine the vascular wall, increased thickness and enhancement of the right internal carotid artery terminal segment and proximal segment of middle cerebral artery were detected (Figure 1.1.2).
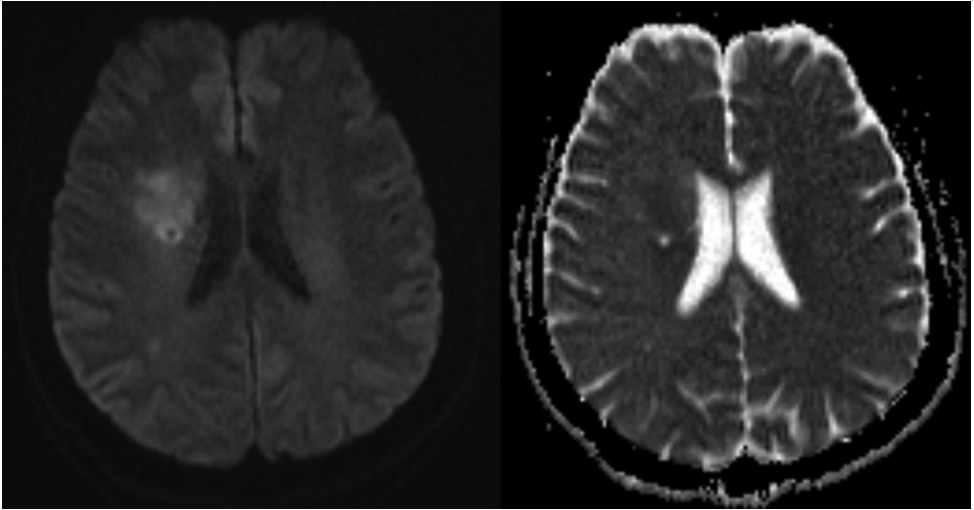
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Figure 1.1.1 DWI-ADC map images showing diffusion restriction in the right basal ganglia and anterior limb of the right internal capsule.
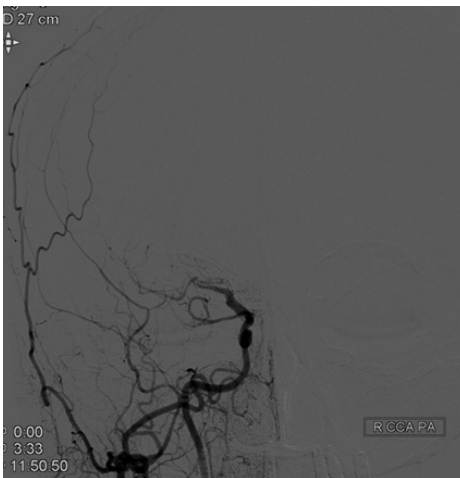

Figure 1.1.2 DSA image demonstrating an occlusion in the right anterior cerebral artery A1 segment and a 50% stenosis in the right middle cerebral artery M1 segment.

She was diagnosed with isolated cerebral vasculitis of the central nervous system and treated with a combination of steroids and azathioprine. After an eight-month follow-up period, partial regression in stenosis in MR angiography, complete resolution in vessel-wall enhancement and partial resolution in wall thickening in VWI MR were observed (Figure 1.1.3).
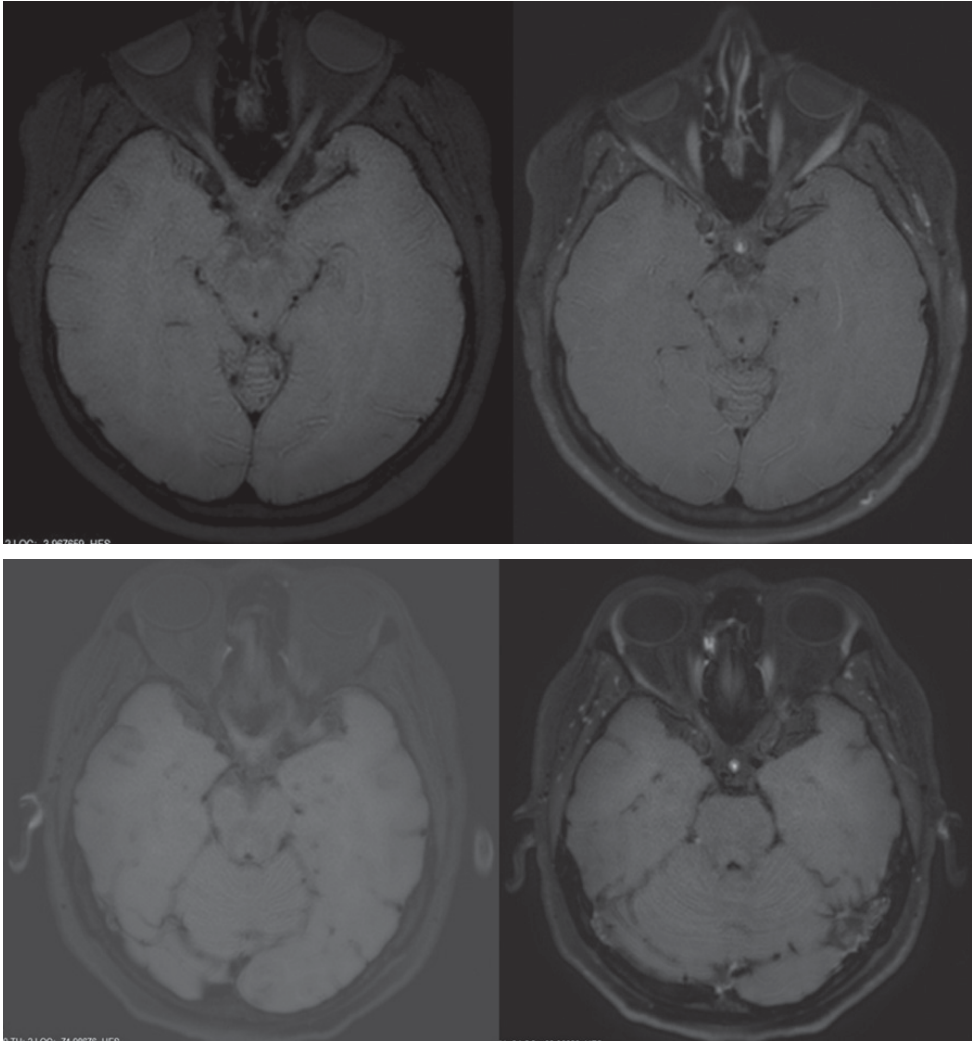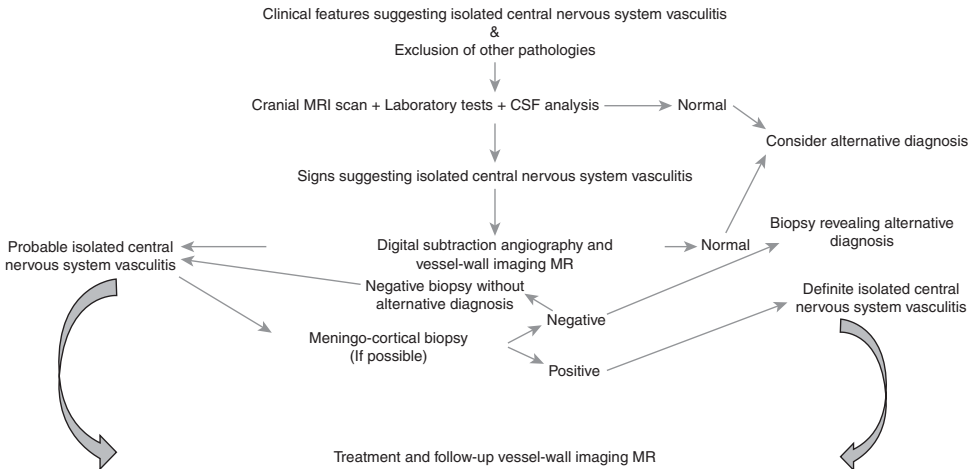
Figure 1.1.3 Vessel-wall imaging showed active inflammation with contrast enhancement in the vascular wall of the M1 segment of the right middle cerebral artery. In follow-up VWI, complete resolution in vessel-wall enhancement and partial resolution in wall thickening were detected.

Clinical features suggesting isolated central nervous system vasculitis
&
Exclusion of other pathologies

Cranial MRI scan + Laboratory tests + CSF analysis ⟶ Normal

Consider alternative diagnosis

Signs suggesting isolated central nervous system vasculitis

Probable isolated central nervous system vasculitis ⟵

Digital subtraction angiography and vessel-wall imaging MR ⟶ Normal

Biopsy revealing alternative diagnosis

Negative biopsy without alternative diagnosis

Negative

Definite isolated central nervous system vasculitis

Meningo-cortical biopsy (If possible)

Positive

Treatment and follow-up vessel-wall imaging MR

Case Discussion

Isolated central nervous system vasculitis (ICNSV) is a rare and poorly understood vasculitis limited to the brain and spinal cord. The cause and pathogenesis of ICNSV have not yet been fully elucidated. Although spinal cord abnormalities are present in approximately 5% of patients, they are rarely seen alone. The thoracic spinal cord is the most frequently affected part of the spinal cord.[1] The annual incidence rate of ICNSV has been reported in the literature as 2.4 cases per 1,000,000 people.[2] Although ICNSV can be seen at any age, it is predominantly seen in the fourth to sixth decades and shows a similar frequency between the genders.[3]

Neurological symptoms in ICNSV can manifest in a broad spectrum, usually consisting of headache, cognitive dysfunction, focal neurological deficit or stroke. Although there is no definitive diagnostic laboratory/serological test for ICNSV, routine biochemical-serological testing and acute-phase reactants, antinuclear antibodies, antineutrophil cytoplasm antibodies and antiphospholipid antibodies should be sought in patients suspected of having ICNSV to exclude secondary causes.[4] CSF analysis is abnormal in 80–90% of pathologically documented ICNSV cases, often having a high protein content and lymphocytic pleocytosis.[5] However, the positive predictive value (37%) and specificity (40%) of abnormal CSF findings are found to be low in the diagnosis of ICNSV.[6]

Long-term survival in ICNSV is found to be decreased, and it has been demonstrated that increased mortality is associated with cerebral infarctions and the involvement of large vessels.[2]

Imaging in Isolated Vasculitis of the CNS

Imaging findings are quite variable, ranging from small ischemic changes to large areas of infarction, hemorrhage, white matter edema and also contrast enhancement. Occlusion, various degrees of stenosis or contrast enhancement at the vessel wall can be detected in the cerebral arteries. Magnetic resonance (MR) imaging is the most common imaging modality in the work-up of patients with suspected ICNSV due to its high tissue contrast and the

various sequences that can be used to visualize different pathological conditions in the context of ICNSV.[7] MRI should be performed with contrast media if possible, and diffusion-weighted imaging (DWI) is required for the detection of acute lesions and also for differentiating acute lesions from chronic lesions. It is also important to include susceptibility-weighted sequences in the MR examination, as susceptibility-weighted imaging (SWI) may demonstrate accompanying microhemorrhages and small vessel involvement.[8] MRI features similar to demyelinating diseases, including cases with bilateral diffuse white matter involvement, may result in diagnostic delay.[9-10] Therefore, if necessary, spinal MR examinations should be performed to exclude demyelinating pathologies such as neuromyelitis optica (NMO) and multiple sclerosis (MS) in terms of differential diagnosis.

Although many studies have reported a high sensitivity of MRI in histologically confirmed cases, MRI findings are not pathognomic.[6,11] In MRI, cortical-subcortical infarcts, parenchymal-leptomeningeal contrast enhancement, intracerebral-subarachnoid hemorrhage, tumor-like mass lesions, supratentorial-infratentorial white matter signal changes in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences can be detected.[11,12] Multiple discrete infarcts are the most common MRI findings in ICNSV.[4] Less frequently in MRI, more specific findings can be detected, such as vessel-wall thickening and intramural contrast enhancement.

It has been demonstrated that the vessel-wall imaging (VWI) MR technique, which has been used frequently in recent years, is more successful in this regard.[13] It has been reported that VWI MR can play an important role in determining an accurate localization for biopsy by identifying inflamed intracranial vessels.[14] The main purpose of performing VWI MR is to differentiate pathologies such as dissection, which results in intramural hematoma, from vasculitis. However, it may not always be possible to distinguish vasculitis from the inflammatory changes in the vascular wall that accompany atherosclerosis.

Given that MRI is abnormal in most cases of ICNSV, the combination of normal MRI and CSF findings has a strong negative predictive value and will exclude the possibility of CNS vasculitis in most patients.[5]

If suspicious findings are detected in MR examination, it will be appropriate to perform MR angiography (MRA) and MR venography (MRV). Although natural findings in MRA do not rule out the diagnosis, it is recommended to perform MRA since vasculitic processes involving large vessels can be recognized by this examination. MRA has limitations, especially regarding the optimal visualization of posterior cerebral circulation and small vessels.[15]

In addition, serial MRI and MRA accompanied by neurological examinations can be used in the follow-up of patients who have been diagnosed with ICNSV.[4]

CT is abnormal in 33–66% of cases and due to its low sensitivity in ICNSV diagnosis, CT should be used only to exclude hemorrhage or when MRI cannot be performed.[5,16] CT angiography (CTA) is also useful for imaging large vessel involvement and may demonstrate stenosis, occlusion, aneurysm and concentric arterial wall thickening in ICNSV.[17] Cerebral digital subtraction angiography (DSA) is considered the most sensitive and is the gold standard imaging modality for the diagnosis of ICNSV, but the findings are not pathognomonic, similar to other radiological modalities.[18] The sensitivity of DSA in the diagnosis of ICNSV was reported to be between 50% and 90%; however, its specificity was found to be low.[4] Findings suggesting ICNSV in DSA include asymmetric narrowings and dilatations with a string of beads appearance along the vessel course, occlusions or stenoses in vascular structures, blurred vascular margins, accompanying aneurysms, formation of collaterals and delayed arterial emptying or prolonged circulation time along the involved

vascular territories.[2,18] Although DSA has higher resolution than cross-sectional angiographic modalities, it does not allow direct evaluation of the vessel wall due to its focused intraluminal imaging.[7,19,20]

Since reversible cerebral vasoconstriction syndrome may simulate ICNSV findings in DSA, complete or nearly complete regression should be seen in control DSA or MRA within 12 weeks of onset of symptoms in cases suspected to have reversible cerebral vasoconstriction syndrome.[4] Flat detector CT angiography (FDCTA) is a novel modality that can be performed in DSA and has superior spatial resolution compared to DSA. FDCTA allows us to track small vascular structures in fine detail, and it is especially important in the evaluation of posterior circulation and brainstem lesions.[21] To avoid false positive results in the diagnosis of ICNSV, angiography and FDCTA results should always be interpreted alongside clinical, laboratory and MRI findings.

Biopsy

Histological confirmation obtained with cerebral and meningeal biopsy samples is the gold standard for the definitive diagnosis of ICNSV.[22,23] In patients where angiography does not provide a diagnosis, biopsy is important, not only to confirm the diagnosis, but also to exclude mimickers of ICNSV.

In determining the accurate localization for biopsy, lesions that show contrast enhancement in MRI or areas with contrast enhancement in the vascular wall in VWI MR can be used, thereby increasing the sensitivity of the obtained specimen for the diagnosis of ICNSV.[14,19] In patients where focal findings have not been detected with radiological modalities, a random biopsy sample should be taken from the anterior tip of the non-dominant temporal lobe.[24] For optimal diagnostic sensitivity, the biopsy sample should include dural, leptomeningeal, cortical and subcortical tissues.[22] Detection of negative results on biopsy does not rule out the diagnosis of ICNSV, as in radiological modalities.

Histopathology is not uniform in biopsy samples obtained from ICNSV patients; however, granulomatous vasculitis is the most predominant histopathological form in ICNSV.[25]

Diagnostic Criteria

ICNSV is a rare disease, and a high degree of clinical suspicion is of great importance for diagnosis. There are several criteria suggested by Mallek and Calabrese in the diagnosis of ICNSV:

1. A history or clinical findings of acquired neurological deficits which has remained unexplained after detailed initial examinations.
2. Classical angiographic findings or histopathological findings compatible with vasculitis within the central nervous system.
3. Lack of evidence showing that angiographic or pathological features are secondary to systemic vasculitis or any other condition.[26]

Treatment

ICNSV is a disease in which clinical findings, radiological features and histopathological analysis results are not uniform, and there are no randomized clinical studies in terms of medical treatment.

As with other vasculitis, high-dose steroids and cytotoxic agents are used in the treatment of ICNSV.[4,27]

Aggressive medical therapy should be initiated rapidly in ICNSV patients with bilateral large vessel involvement, multiple and recurrent cerebral infarctions, and a progressive clinical course. Unfortunately, in these cases, response to treatment is poor and the disease usually leads to a grave prognosis.[28]

ICNSV cases who have small vascular involvement accompanied by leptomeningeal enhancement on MRI are generally diagnosed using brain biopsy, since there is no finding in DSA (Figures 1.1.4 and 1.1.5). In this subset of patients, the response to the medical treatment is better, and their clinical course is more favorable.[29,30]

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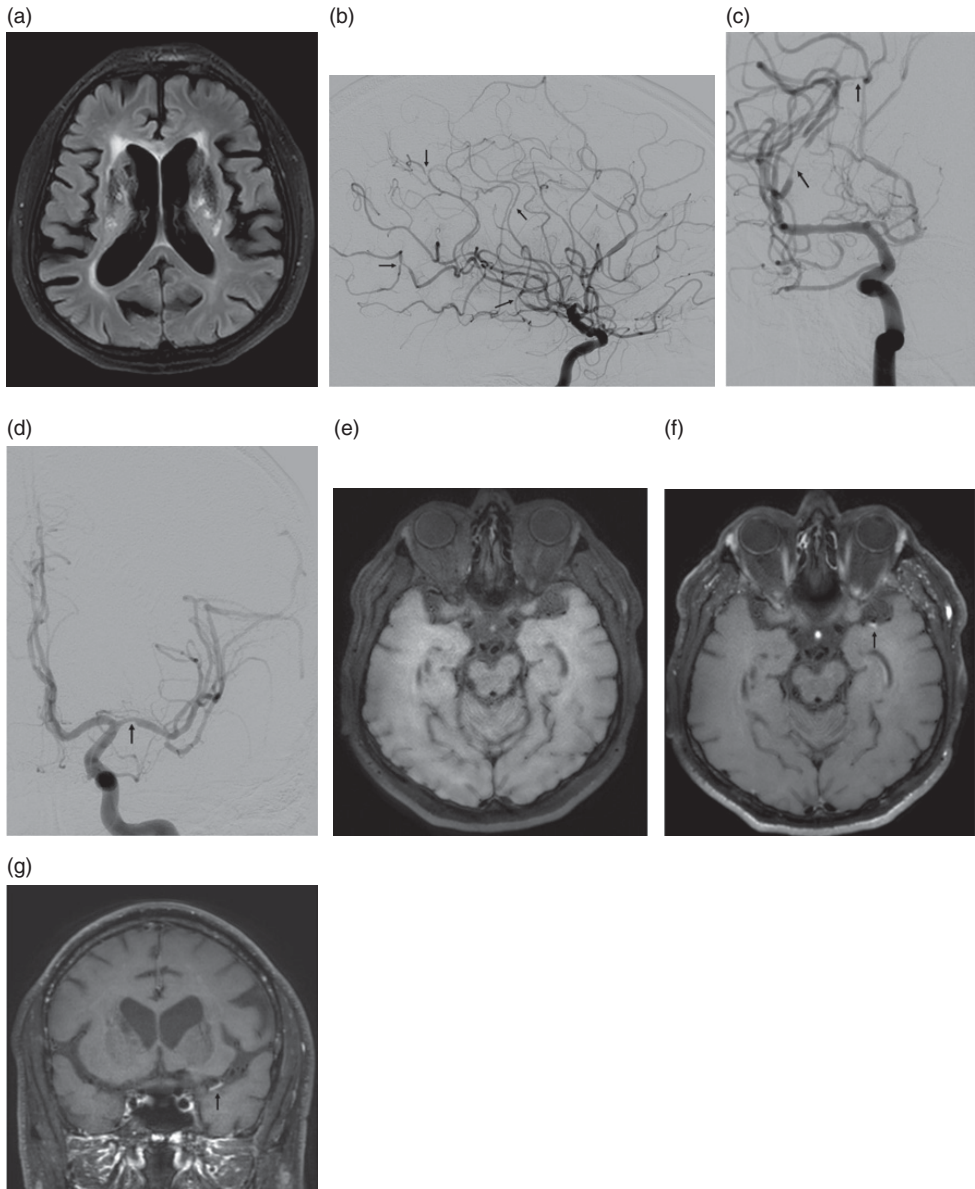
Figure 1.1.4 (A) Axial FLAIR MRI shows multiple chronic ischemic lesions in the bilateral basal ganglia and periventricular white matter. (B–D) DSA images of the same patient. (B–C) demonstrate asymmetric involvement (black arrows) in the right middle and anterior cerebral artery branches. (D) shows asymmetric involvement (black arrow) in the M1 segment of the left middle cerebral artery. (E–G) Vessel wall imaging MR images of the same patient. (F) and (G) demonstrate active inflammation with contrast enhancement in the vascular wall of the M1 segment of the left middle cerebral artery (black arrows).
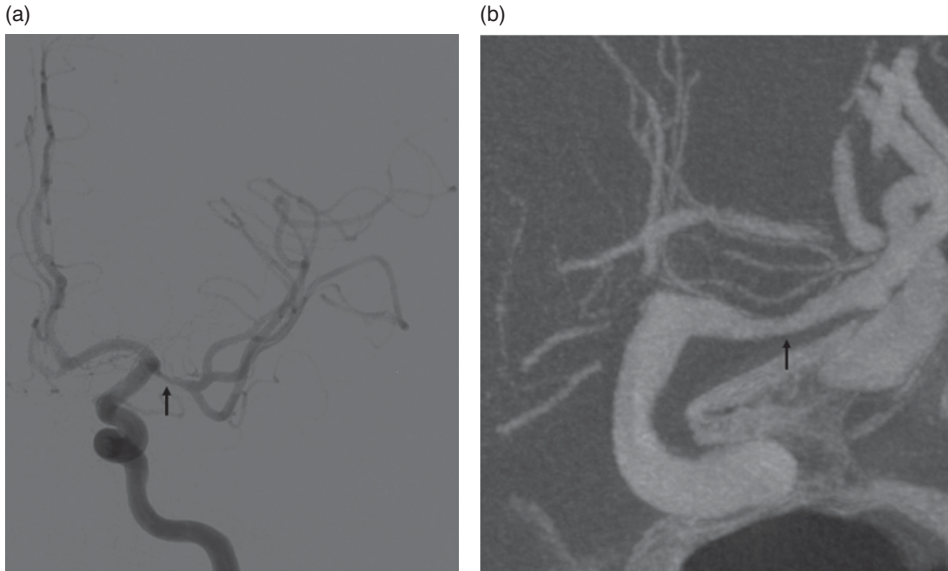
(a)   (b)

Figure 1.1.5 (A) DSA image following left ICA injection shows the narrowing of the M1 segment of the left middle cerebral artery (black arrow). (B) Oblique maximum intensity projection image of left middle cerebral artery obtained with Flat Detector CT Angiography demonstrates the narrowing secondary to isolated CNS vasculitis (black arrow).

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