Diagnostic Dilemma in A Man Who Presented with Headache and Transient Memory Loss

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Interesting case

A 60-year-old man, retired, lives in the Nakhon Ratchasima province.

Chief complaint

Sudden onset headache with transient confusion for 1 day

Present illness

Five days before admission, he had a headache coming up immediately in the center of the head. The headache was sudden onset without radiation to other sites and severe exacerbations within 2-3 minutes accompanied by nausea. The pain occurred while at rest (10-point of visual analog scale) without any pre-monitory symptoms but when coughing made the headache worse. The headache disappeared on its own without any treatment. No photophobia or phonophobia, blurred vision and any limbs weakness.

One day before admission, he had severe headache in the second time in the same site. The pain severity was aggravated to a severe intense level within the same amount of time without precipitating symptoms. His wife said he was transient memory impaired at times while having a recurring headache. No neck pain, no loss of conscious, no dysarthria and no abnormal sensation associated with the headache.

Past illness

He was diagnosed with high blood pressure but had not been treated.

No alcohol consumption and quit smoking for 5 years

Refuse to use vasoconstrictive drugs compound

No history of migraine

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Family history

Unknown coronary heart disease in his family

Physical examinations

General appearance: A Thai aged man, alert but disoriented to time

Vital signs: BT 37.2 C, HR 90 bpm regular, RR 20 bpm, BP 180/70 mmHg

HEENT: pink conjuctiva, anicteric sclera, no skin lesion, no lymphadenopathy, no thyroid gland enlargement, absent carotid bruit

Heart and Lungs: unremarkable

Abdomen: soft, not tender, no hepatosplenomegaly

Extremities: no pitting edema, no rash

Neurological examination: E4V5M6, alert, orientation to time, place and person

Cranial nerves: CN I: normal, **CN II:** pupil 2 mm RTLBE, no RAPD, no visual field defect, **CN III, IV, VI:** extraocular muscles movement were intact, **CN V:** normal mastication muscles, intact corneal reflex, intact pin prick and temperature sensation, **CN VII:** no facial droop, complete closed eyes, **CN VIII:** normal, **CN IX, X:** equally palatal movement, positive gag reflex, **CN XI:** head turning and shoulder shrug were intact, **CN XII:** no tongue atrophy, normal tongue movement

Motor: no muscle atrophy, no fasciculation, normal muscle tone, motor power grade V/V both sides

Sensory: intact pin prick, fine touch and proprioception

DTR: 2+ all limbs

Cerebellar signs: intact FTNF, no dysdiadochokinesia, normal gait

Babinski sign: plantar response

Clonus: negative

Meningeal signs: negative

Speech examination: normal motor speech, comprehension and repetition

TMSE: 28/30 (impaired three-things recall), MOCA test: incomplete examination at admission but 28/30 in the next day (impaired recall).

Positive findings

1. Thunderclap headache
2. Transient memory impaired
3. Hypertension

Investigations (At admission)

Complete blood count: Hb 13.4 g/dL, Hct 38.7%, WBC 7,400 /uL (PMN 64%, L 26%, Mono 6%, E 4%), Plt 141,000 /uL, MCV 80.2 (80-98) fL, MCH 27.4 (25.6-32.2) pg/cell, MCHC 34.2 (32.2-36.5) g/dL, RDW 13.6% (11-14)

Chemistry: BS 101 mg/dL, BUN 13.7 mg/dL, Cr 1.05 mg%, Na 140 mmol/L, K 4.2 mmol/L, Cl 104 mmol/L, CO_2 24 mmol/L, Ca 9.2 mg/dL, P 2.8 mg/dL, Mg 2.2 mg%

Liver function test: TP 8.2 g%, Alb 4.4 g%, Glb 3.8 g/dL, TB 0.4 mg%, DB 0.2 mg%, AST 17 U/L, ALT 23 U/L, ALP 84 U/L

Lipid profile: CHO 203 mg%, TG 134 mg%, HDL 37 mg%, LDL 139.2 mg%

Anti-HIV: non-reactive, **ANA:** negative, **VDRL:** non-reactive, **ESR:** 8 mm/hr

EKG: normal sinus rhythm, rate 85/min regular, no ischemic pattern, no chamber enlargement

CXR: normal cardio-thoracic ratio, normal parenchymal of both lungs

CSF analysis: OP 16 cmH_2O, clear, colorless, no WBC, RBC 10 cell/mm^3, protein 40 mg/dL, normal glucose ratio

Discussion

An elderly male patient had an acute, severe headache in the first attack. He also had transient

memory dysfunction and nausea while having a headache. The neurological examinations revealed no significant abnormalities. The headache characteristic was an extremely severe intensity in a short period of time. The secondary headache was concerned in the patient's problem. The possible diagnosis include: intracranial vascular disorders (hemorrhage, inflammation, thrombosis), localized pachymeningitis, intracranial mass, pituitary apoplexy, cerebral vasospasm and cerebral venous sinus thrombosis. Blood test results were normal, except hypercholesterolemia. Neuroimaging studies were demonstrated in the figures.

Neuroimaging: At admission (in Figure 1-4)

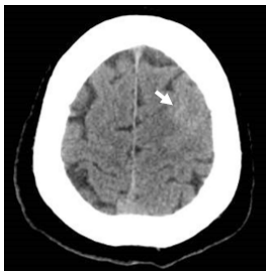

Figure 1 Initial non-contrast CT brain axial view showed thin subarachnoid hemorrhage (SAH) at left high frontal lobe region (*white arrow*)

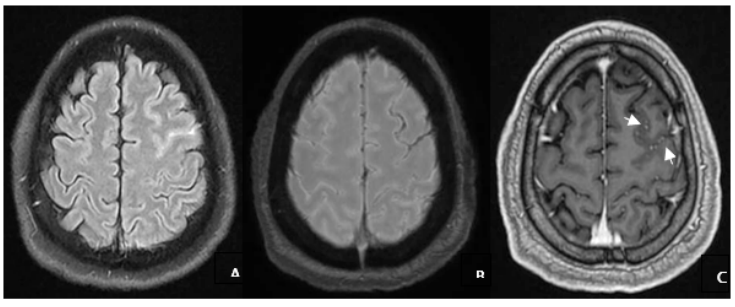

Figure 2 MRI brain showed thin SAH at left high frontal lobe region on axial FLAIR fat suppression image (A) with blooming artifact on axial SWI (B). Axial 3D T1W post gadolinium administration showed leptomeningeal collateral at the left frontal lobe sulci, where the SAH was found (C). (front cover)

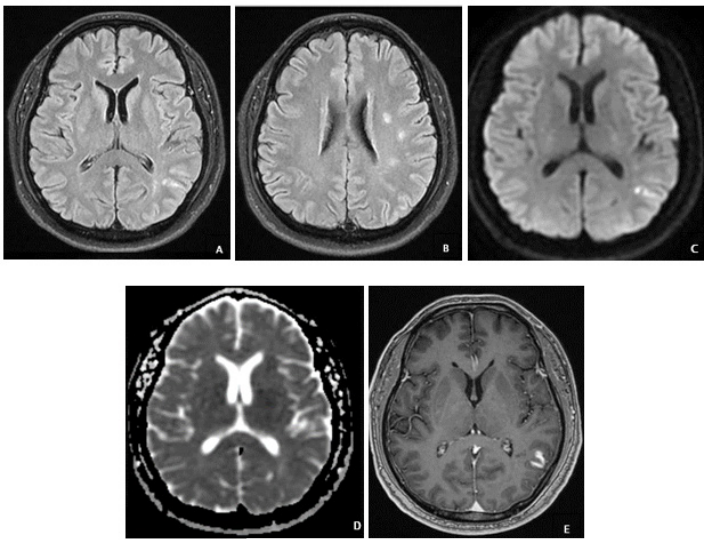

Figure 3 MRI brain showed hyper SI at the left parietal cortex on axial FLAIR FS image(A) without restrict diffusion on axial DWI (C) and ADC (D) images. Axial 3D T1W post gadolinium administration showed gyral enhancement at this region (E). Lacunar infarctions at corona radiata of the left frontoparietal region were present on the axial FLAIR FS image (B). (front cover)

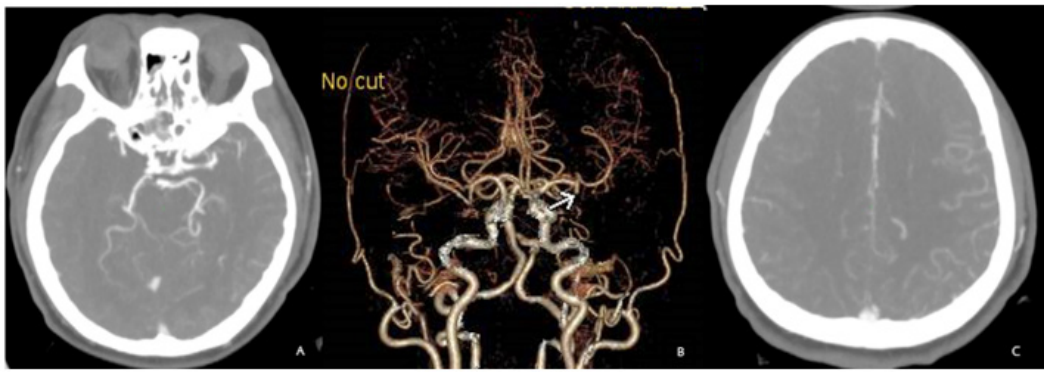

Figure 4 CT angiography showed abrupt tapering at the inferior branch of left M1 MCA post bifurcation segment on axial MIP CTA (A) and 3DVRT (B). Relatively increase cortical vasculature was found in axial MIP CTA (C).

Management

After the initial neuroimages, the possible diagnoses include: primary angiitis of the CNS (PACNS), CNS vasculitis and reversible cerebral vasoconstriction syndrome (RCVS). He was treated with antihypertensive medication by calcium channel blocker. A few days later, his headache improved (from 10-point to zero of VAS) and no residual neurological symptoms. He was discharged from the hospital within two weeks and his blood pressure was controlled between 120/70 to 130/80 mmHg. The antihypertensive and lipid lowering agents were given to be taken at home. He was advised to observe headaches and neurological disorders.

About 3-month follow up at OPD, he had no more headaches, no limb weakness, no visual dysfunction or other neurological deficits. His blood pressure was 135/70 mmHg. The neurological examinations were intact. The TMSE and MOCA test were 30/30 point at all. The follow up neuroimages were shown in the Figure 5.

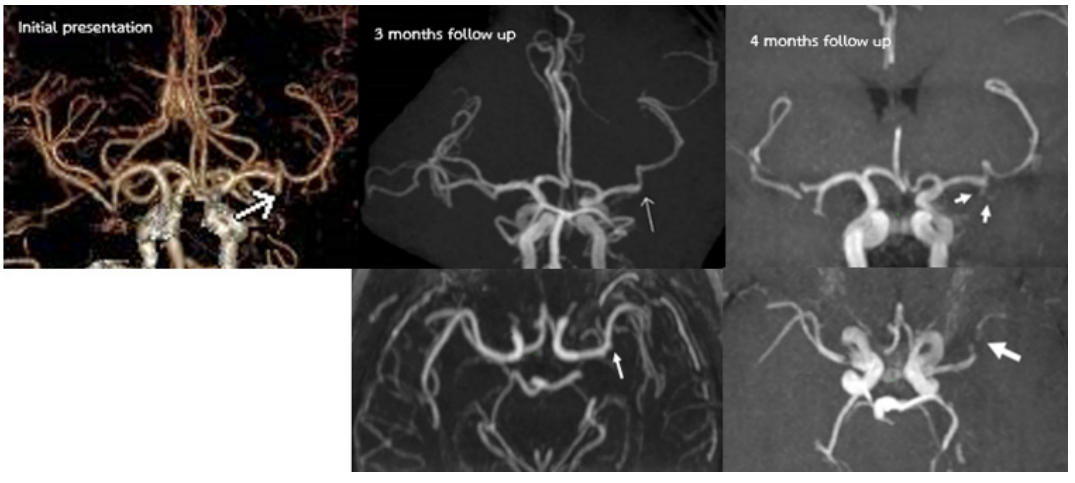

Figure 5 Follow-up imaging on 3 months and 4 months showed more recanalization of the inferior branch of left M1 MCA post bifurcation segment but still visualized stenosis.

Diagnostic dilemma

From a radiologist's perspective, the initial image finding of isolated acute nontraumatic cortical subarachnoid hemorrhage[1], stenosis of the inferior branch of the left M1 MCA post bifurcation segment and no evidence of arterial aneurysm or cortical venous thrombosis (Figure 1-4) raised concern of RCVS. However, the stenosis segment of the post-bifurcation left M1MCA was a quite long segmental, non-beaded and single location that do not follow RCVS imaging criteria.[2] Other differential diagnoses such as PACNS, CNS vasculitis, intracranial atherosclerotic vascular disease (ASVD), arterial dissection and thrombosis were included.

Interestingly, the area where the SAH was shown, also seen leptomeningeal collateral (Figure 2) and increased cortical vasculature at high left frontoparietal lobes (Figure 4) could be the clue that these areas were impending infarction with compensatory leptomeningeal collateral.[4,5] Additional findings of some lacunar infarctions at the left frontoparietal lobes and subacute cortical infarction at the left parietal lobe might support the hypothesis (Figure 3). Unfortunately, our institute cannot perform high-resolution vessel wall imaging[3] to characterize vessel wall disease at the post bifurcation left M1MCA and arterial nearby the left frontal lobe where the subarachnoid hemorrhage was found, no available cerebral angiography[3] and cannot perform perfusion imaging for evaluating brain perfusion at this region. As described are our limitations.

Follow-up MRA brain showed more recanalization of the inferior branch of left M1 MCA post bifurcation segment in the latest study on 4 months after the onset of disease but still visualized stenosis (Figure 5) which was probably to be vasculitis or primary angiitis of the CNS or recanalization of the occluded lumen from stroke or dissection. Less likely to be RCVS of the post bifurcation left M1 MCA due to lack of reversible within 12 weeks after onset criteria.[2] However, no definite evidence that subarachnoid hemorrhage at the left frontal region was the same or different etiology from the stenosis of the post bifurcation left M1 MCA.

From a neurologist's perspective, the provisional diagnosis in this patient suspected RCVS supported by thunderclap headache, non-traumatic convexity SAH and even if found incomplete of reversible vasospasm in follow up imaging. Although it was not a clear precipitating factors with the vasoconstrictive agents. The absence of evidence of inflammation in the CNS lead to less thinking about the inflammatory process. Interestingly, his clinical symptoms returned to normal with full recovery without residual neurological deficits.

Review RCVS

RCVS is used to describe a multitude of pathologies encompassing the clinical terms thunderclap headache with reversible vasospasm.[6-8] The diagnosed based on key clinical features of thunderclap headache or severe recurrent headache, cerebral vasoconstriction on imaging in at least 2 different arteries and resolution of vasoconstriction by 3 months.[9,10] RCVS is possibly caused by a transient dysregulation of cerebral vascular tone, leading to multi-focal arterial constriction and dilation.[8] The main clinical manifestation is recurrent sudden-onset and severe (thunderclap) headaches over 1–3 weeks, often accompanied by nausea, vomiting, photophobia,

confusion and blurred vision.[9,11] The major complications are localized convexity non-aneurysmal subarachnoid hemorrhage (22%) and ischemic stroke or intracerebral hemorrhage (7%), which may leave permanent residual neurological deficits.[12,13] The evidence to suggest that many factors associated with vasospasm from subarachnoid hemorrhage including catecholamines, endothelin-1, calcium, serotonin, nitric oxide and prostaglandins may play a similar role in the pathophysiology of vasoconstriction in RCVS.[6,8,9] Blood-brain barrier breakdown is another proposed mechanism of RCVS, given the pathophysiological mechanisms of sympathetic overactivity and dysregulation of cerebrovascular tone.

In a study comparing 110 patients with PACNS to 173 patients with RCVS, 70% of RCVS patients had a precipitating factor (drug induced, alcohol consumption, direct vascular injury and physical/sexual activity). Parenchymal imaging by cranial CT or MRI was abnormal in all PACNS patients and in only 31% of RCVS patients.[14] There are multiple imaging modalities used in the diagnosis, monitoring, and management of RCVS. Luminal and parenchymal biomarkers of RCVS have been established, whereas other imaging findings bare associations in the context of the clinical diagnostic criteria for RCVS.[7,14] Cerebral catheter digital subtraction angiography (DSA) is considered the gold standard in visualizing vasoconstriction and detecting abnormalities, especially in distal vessels with a sensitivity of 100% with 2-dimensional DSA. Compared with the gold standard, CTA and MRA both share a detection sensitivity of about 80% in RCVS-related cerebral vasoconstriction.[14] Cranial CT and CTA can effectively screen for non-aneurysmal cortical/convexity SAH, an early parenchymal biomarker of RCVS when capture of vasoconstriction lags which is the same as seen in this patient. Also found that presence of hyperintense vessels on MRI fluid-attenuated inversion recovery have been hypothesized to be a biomarker for RCVS because they are a result of abnormal flow in small vessels. In a study of 95 patients with RCVS, 22.1% had HI with significantly higher MCA and PCA.[15] The difference characteristics between RCVS and PACNS are shown in the table 1.

Table 1 The difference characteristics between RCVS and PACNS

Characteristics	RCVS	PACNS
Symptoms develop	rapidly	more slowly
Headache onset	severe abrupt	gradual
Associated neurological deficits	Confusion, seizure, blurred vision, cognitive deficit	same RCVS
CSF analysis abnormalities	minimal	90% or more
Neuroimaging abnormalities	less frequent	more frequent
Reversibility within 3 months	more frequent	less frequent
Clinical prognosis	self-limited	progressive

Conclusion

The combination of both clinical history and diagnostic imaging remains crucial to not only include a diagnosis between RCVS and PACNS but also to exclude other diagnoses that require different treatment strategies.[16-18] It is important to follow up with the patient if the persistent cerebral

vasoconstriction. Imaging modality selection should be based on anticipated diagnostic and therapeutic benefit balanced by patient-specific safety concerns. I really hope that there will be more systematic reviews and RCT trials to support the exact pathogenesis and criteria for the diagnosis for RCVS in the future.

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