A Case Report of Thunderclap Headache with Sub-arachnoid Hemorrhage and Negative Angiography: A Review of Call-Fleming Syndrome and the use of Transcranial Dopplers in Predicting Morbidity

Abstract

Introduction: We present a case report in a patient with severe, recurrent, thunderclap with computed tomography (CT) evidence of subarachnoid blood and negative work-up for aneurysm. This case is an example of Call-Fleming syndrome with subarachnoid hemorrhage in which transcranial Doppler (TCD) was used for monitoring of cerebral vasoconstriction when angiography did not evidence vasoconstriction. We will review Call-Fleming syndrome and the utility of transcranial doppler imaging to assess cerebral vasoconstriction.

Methods: A review of the current literature regarding diagnostics, treatment, and morbidity in Call-Fleming (reversible cerebral vasoconstriction syndrome) as well as a review of the data using transcranial color-coded sonography and transcranial doppler imaging to assess vasospasm in these cases.

Results: The patient underwent computed tomography angiography (CTA) and venography (CTV), catheter angiography, lumbar puncture, and vasculitis work-up which were all negative. His magnetic resonance imaging (MRI) showed T2 weighted and fluid attenuation inversion recovery (FLAIR) hyper-intensities in the posterior frontal lobes as well as subarachnoid blood along bilateral occipital convexities. TCDs were obtained which showed elevated mean velocities.

Conclusion: The use of bedside transcranial doppler imaging is a non-invasive means of assessing vasospasm in Call-Fleming syndrome; even in cases where angiography is negative. Determining the degree of vasospasm based on the data in subarachnoid hemorrhage, we are able to predict a patient's risk of complications related to vasospasm including reversible posterior leukoencephalopathy and ischemic events.

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Introduction

We present a case report in a patient with severe, thunderclap headache twice in three days with CT evidence of subarachnoid blood after the second event and negative work-up for aneurysm. Based on the headache presentation and negative work-up, this case is an example of Call-Fleming syndrome with subarachnoid hemorrhage in which transcranial doppler imaging was used for monitoring of cerebral vasoconstriction (evidenced by increased mean velocities) when angiography did not evidence vasoconstriction. We will review Call-Fleming syndrome and the utility of transcranial doppler imaging to assess cerebral vasoconstriction.

A 56 year old man was transferred to the University of Kansas medical center from a community hospital emergency department after re-presenting for "worst headache" of his life as well and new onset seizure activity witnessed by EMS. Head CT after this event showed left parietal convexity subarachnoid hemorrhage. The patient had similar episode of "thunderclap" headache three days prior with normal CT of the head and without lumbar puncture evidence (Table 1) for subarachnoid hemorrhage or meningitis at outside emergency room. Both headaches were described as acute, maximal intensity at onset, worst headache of his life, causing him to fall from standing due to severity. The first event occurred at work and second while at home in the shower.

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Table 1: Patient's spinal fluid analysis.

WBC	0 cells/μL
RBC	0 cells/μL
Protein	34 mg/dL
Glucose	70 mg/dL

Table 3: TCD criteria for SAH induced vasospasm(15)

Cerebral Blood Flow Velocities	Degree of Vasospasm
30-80 cm/sec	normal
120-140 cm/sec	mild
140-200 cm/sec	moderate
>200 cm/sec	severe

Table 2: Patient's TCD data.

Vessel	Depth	Left Mean	Right Mean
MCA	50	111	119
MCA/ACA	60	106	88
ACA	65	-72	-71
PCA	65	27	-44
Ex ICA	50	-40	-44
VA	65	-35	-33
BA	80	-36	
Lindegaard indices		2.74	2.69

Past medical history included hypertension, hyperlipidemia, migraine headaches, and cervical stenosis. He had no history of tobacco, alcohol, or illicit drug use. His medications included benzapril, simvistatin, and oxycodone. His neurologic exam was positive for diffuse hyperreflexia, mild left hemisensory changes, and non-sustained clonus at both ankles.

On arrival, the patient was loaded with fosphenytoin for seizure activity. There was no laboratory evidence of coagulopathy with international normalized ratio (INR) of 1.0 and activated partial thromboplastin time (aPTT) of 29.0 seconds. Sedimentation rate and C-reactive protein were within normal limits. Systolic blood pressure was elevated to 190 mmHg and the patient required blood pressure control with intravenous nicardipine. The patient underwent CT angiography and venography which were negative for aneurysm or thrombus. MRI was obtained that revealed a small amount of subarachnoid hemorrhage along the posterior occipital convexities bilaterally and small focus of enhancement in the left parieto-occipital lobe (Figure 1). Several small FLAIR and T2 hyperintensities in the high frontal lobes bilaterally were noted on MRI as well (Figure 2). A 4-vessel angiogram of head and neck was obtained and was negative for aneurysm, stenosis, occlusion, or arterio-venous malformation. The patient underwent bedside transcranial doppler studies which showed elevated mean velocities.

With the patient's sudden thunderclap headache, the clinical scenario was consistent with the Call-Fleming syndrome and this was suspected initially. Further work-up ruled out other conditions including aneurysmal SAH, vasculitis, meningitis, and cerebral venous sinus thrombosis.

Background:

Reversible cerebral vasoconstriction syndromes (RCVS) also referred to as Call-Fleming syndrome, is best characterized by "reversible, multi-focal narrowing of the cerebral arteries heralded by sudden (thunderclap), severe headaches with or without neurologic deficits".[1] This syndrome is usually self-limited with resolution of headaches and vasoconstriction that occurs over a period of days to weeks (generally seen within 12 weeks). It is most common in women and associated with the illicit and certain prescription drugs, pregnancy/puerperium, migraine and even bathing.[2,3]

In a prospective series of 67 patients with RCVS by Ducros et al, the pattern of presentation was multiple thunderclap headaches recurring over an average period of one week in 94% of patients. Various complications were observed, with different time courses, including cortical subarachnoid hemorrhage (22%), intracerebral hemorrhage (6%), seizures (3%), and reversible posterior leukoencephalopathy (9%), most of which presented within the first week.[4]

Diagnosis/Differential:

Call-Fleming syndrome is a diagnosis of exclusion (no validated criteria for diagnosis has yet been determined) and generally requires normal cerebrospinal fluid and radiographic evidence of segmental cerebral vasoconstriction which usually affects the medium size arteries. Therefore, vasoconstriction is typically seen in the circle of Willis, but has been documented in all vascular distributions. However, with the variability in resolution of cerebral vasoconstriction, the classic imaging findings are not necessarily seen in all cases and, if absent, may be a good prognostic indicator.[5] Non-invasive imaging commonly used to evaluated cerebral vasculature include magnetic resonance angiography (MRA), computed tomography angiography (CTA), and transcranial doppler ultrasonography (TCD). The gold standard imaging modality is catheter based angiography to

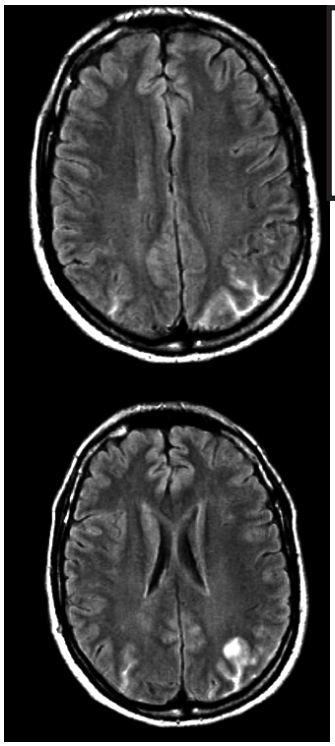

Figure 1: MRI findings: Small subarachnoid hemorrhage along the posterior occipital convexities and small focus of enhancement in the left parieto-occipital lobe.

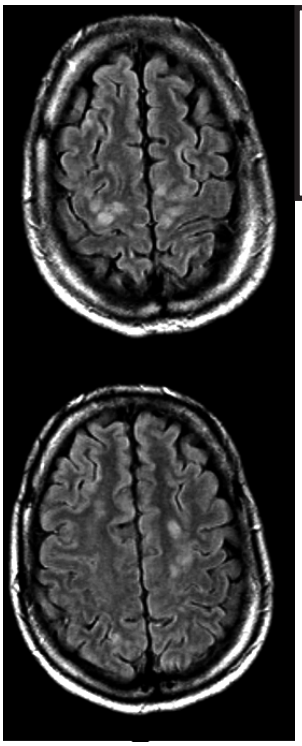

Figure 2: MRI findings: Several small patchy FLAIR and T2 hyperintensities in the high frontal lobes bilaterally.

detect vasoconstriction.

In the differential of thunderclap headache are other causes of cerebral vasoconstriction including vasculitis and dissection. Aneurysmal SAH, cerebral venous sinus thrombosis, hypertensive encephalopathy/PRES, and spontaneous intracranial hypotension should be considered in the differential diagnosis as well.

Treatment:

Treatment of reversible cerebral vasoconstriction syndrome is currently empiric. If provoking agent is determined, discontinuation can be curative. Calcium channel blockers initiated orally have been successful in treatment of symptoms (headache) and shown objective improvement in vasospasm on repeat neuroimaging.[6] In fact, several case reports can be found regarding progressive neurologic deterioration and the emergent use of intravenous or intra-arterial nimodopine.[7] Dantrolene, which acts as a muscle relaxer by inhibiting calcium release by the sarcoplasmic reticulum, has shown benefit in reducing vasospasm evidenced by serial TCDs.[8] Positive outcomes have been reported when treating this condition like migrainous and subarachnoid induced vasospasm, i.e. with non-steroidal anti-inflammatory agents and magnesium sulfate.[9]

Brief courses of glucocorticoids have documented improvement in vasopasm as well; this was typically seen when RCVS was presumed to be and treated like angiitis.[10] Recurrence of cerebral vasoconstriction with or without treatment is not well reported and in the series reported by Ducros, none of the 67 patients experienced a relapse.

Utility of TCD imaging:

Chen et al described the use of transcranial color-coded sonography in a series of thirty-two patients with Call Fleming syndrome and reported elevated mean maximal velocities of 109.5 ± 30.8 cm/sec with LI of 2.2 ± 0.7 which exceeded the control findings of 66.3 ± 9.5 cm/sec with LI 1.4 ± 0.3. Interestingly mean velocities were still elevated at 3 weeks after headache resolution. And, in patients with mean velocities ›120cm/sec or LI ›3 a greater risk of posterior leukoencephalopathy and ischemic events was reported. Notably, there was no difference in velocities after treatment with nimodipine.[11]

In reference to our case, CTA and catheter angiography did not reveal vasoconstriction; however, bedside TCDs showed bilateral elevated mean MCA velocities and elevated Lindegaard indices (Table 2). Of note, follow-up MRA one month later in this patient revealed smaller caliber left MCA vasculature as compared to the right.

Though there are no diagnostic criteria for RCVS using TCCS, Chen notes using validated criteria for SAH induced vasospam and TCDs,[12] then using that data to infer values that could predict patients with RCVS at risk for ischemic events. When comparing TCD and TCCS, Swiercz et al found in a prospective series of 111 patients that for the diagnosis of ›50% MCA narrowing, sensitivity of the TCCS was similar to that of the TCD but TCCS outperforms conventional TCD in detection of ≤50% MCA narrowing.[13] Based on the criteria for SAH (Table 3), the mean velocities and LI seen in RCVS are less elevated than those seen in SAH but still result in significant morbidity in the form of ischemic event and PRES.[14]

A recent study by Chen et al, regarding the use of repeat MRA

imaging in monitoring progression and resolution of cerebral vasoconstriction in RCVS, mirrors the findings in TCCS imaging by the same authors.[14] Both studies indicate that more severe and pervasive the vasospasm, the higher the risk of PRES and ischemic events.

In summary, though our patient did not have vasoconstriction on CTA and catheter angiography, his TCD studies showed elevated mean velocities and Lindegaard indices in the setting of thunderclap headache with MRI findings of PRES and cortical subarachnoid blood. An extensive work-up for vasculitis, thrombosis or aneurysm was negative. Utilizing the data for mild vasoconstriction in the setting of SAH indicated he was at a higher risk for developing significant complications, which he did. Therefore, in patients with sudden, thunderclap headache, RCVS should be considered while ruling-out other diagnosis such as aneurysm, vasculitis, and aneurysmal rupture which have a similar initial presentation. In these patients, TCDs may offer a non-invasive means to confirm RCVS. Furthermore, TCD information about the severity of the vasospasm based on velocity measurements can allow for risk stratification. Lastly, serial TCD monitoring can help track disease progression.

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