False-Negative Magnetic Resonance Angiography with Extracranial Internal Carotid Artery Stenosis: A Report of Two Cases and Review of the Literature

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Abstract

Magnetic resonance angiography (MRA) is increasingly used as a noninvasive means to assess internal carotid artery (ICA) stenosis. When used alone, however, MRA may not be sufficiently accurate in certain settings to determine whether ICA disease meets surgical criteria. Although MRA has been recognized to overestimate the degree of stenosis, the authors present 2 cases in which it severely underestimated arterial stenosis. Two male patients, 70 and 40 years old, respectively, were admitted with crescendo transient ischemic attacks. Their MRA studies suggested nonsurgical lesions of the ICA. After the patients continued to demonstrate clinical evidence of embolic disease, digital subtraction angiography (DSA) was performed on one patient and the other received a gadolinium contrast-enhanced MRA. These tests revealed critical stenosis in each patient. Both patients were taken to the operating room for awake carotid endarterectomy with heparin anticoagulation and EEG monitoring. At surgery, both patients were found to have severely stenosed ICAs with complex plaques. MRA to determine whether ICA stenosis meets surgical criteria may not be sufficiently accurate in certain clinical settings. Additional imaging studies, such as confirmatory digital ultrasonography, MRA with gadolinium contrast, or DSA may be required to determine the extent of carotid artery stenosis accurately.

Key Words: ICA stenosis, MR angiography, TIA

Running Title: False Negative MRA with Carotid Stenosis

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Introduction

Magnetic resonance angiography (MRA) is increasingly being used as a noninvasive means to assess carotid artery stenosis. MRA is a noninvasive modality that is considered very accurate in the determination of whether internal carotid artery (ICA) disease is surgical or nonsurgical. However, as suggested by the cases presented here, MRA may have limitations that require further studies to quantify stenosis prior to making a surgical decision, especially when the clinical presentation does not correspond with the MRA results.

Case One

A 70-year-old man presented to an outside hospital emergency department with 8 hours of visual disturbances, weakness, and gait ataxia. His previous medical history is significant for a left middle cerebral artery (MCA) stroke suffered 17 years prior to this presentation that resulted in a subtle expressive dysphasia. The patient's wife reported that her husband demonstrated mental confusion, slurred speech, and difficulty with ambulation, and that he had struck the curb several times while driving earlier that day. An initial evaluation with noncontrast head computed tomography (CT) scan, cardiac enzymes, and EKG was normal. The patient reported complete resolution of symptoms while in the outside hospital ER. He was transferred to our institution the next morning for further evaluation and management.

Carotid duplex ultrasound and magnetic resonance imaging (MRI)/MRA of the carotid arteries were obtained. The carotid duplex ultrasound revealed an irregular moderate-to-severe plaque of the right ICA (RICA), although hemodynamic velocities measured in this vessel suggested 50-60% stenosis. Moderate plaque was detected in the left ICA (LICA), but it was not thought to be hemodynamically significant. Both vertebral arteries demonstrated anterograde flow. Three-dimensional time-of-flight (3D TOF) MRA was performed on the day of admission.

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This study, although somewhat limited by motion artifact, was interpreted as normal (Fig. 1). The patient continued to demonstrate clinical findings of embolic disease despite full heparin anticoagulation. On hospital day number three, the patient was re-imaged with 3D TOF MRA, followed by a high-resolution gadolinium-enhanced study evaluating the aortic arch to the skull base. The contrast-enhanced (CE)-MRA study revealed an irregular, circumferential stenosis of the proximal 1.5 cm of the RICA estimated as 40 percent of the vessel (Fig. 2). The unusual plaque configuration, however, made accurate stenosis estimates difficult.

The patient was taken to the operating room for awake carotid endarterectomy with constant heparin infusion, which was performed under local anesthesia. At surgery, a complex, circumferential plaque with near total occlusion of the ICA was discovered. Pathological evaluation confirmed that the atheroma was extensively ulcerated with some calcifications. Post-operatively, the patient was continued on aspirin therapy and had no further embolic events. Three- and six-month follow-ups revealed no further events.

Case Two

A 40-year-old, previously healthy man awoke at 3 a.m. with acute onset of severe left frontal/temporal headache that persisted and increased throughout the course of the day. His wife noted that he frequently used the wrong words in conversation and that he seemed confused at times. He reported an inability to read during the afternoon on the day of his headache and that he had considerable difficulty understanding what people were saying to him. That night, he presented to an emergency room where a noncontrast head CT scan demonstrated a left MCA infarction. He was transferred to our institution for further evaluation and management.

On physical examination, the patient was alert and oriented. He had no dysarthria, although he demonstrated several paraphrasic speech errors and difficulty with repetition. His

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cranial nerves were normal, as were motor, sensory, reflex, gait, and cerebellar function. He was admitted to the Neurology Stroke service for complete evaluation and management.

Brain MRI showed changes consistent with nonhemorrhagic acute left MCA infarction. There was loss of the normal signal void within the left supraclinoid carotid artery, suspicious for stenosis or thrombosis. An MRA demonstrated moderate focal narrowing of bilateral proximal ICAs, moderate diffuse loss of normal signal within the distal LICA, and diffuse irregularity of the right vertebral artery (Fig. 3). A 4-vessel cerebral angiogram was performed, which revealed a normal RICA and severe short segment focal stenosis at the origin of the LICA with possible localized intraluminal thrombus (Fig. 4). Diminished flow in the left MCA from the LICA was noted, with some collateral flow from the contralateral side via the anterior communicating artery and from the ipsilateral posterior circulation via the posterior communicating artery.

The patient was fully anticoagulated on heparin and transitioned to Coumadin. His symptoms resolved within 2-3 days, and he was discharged with a normal neurologic exam. He was allowed to recover from his stroke for 4 weeks prior to planned carotid endarterectomy with EEG monitoring. At surgery, an ulcerative complex plaque causing near total occlusion of the proximal LICA was removed. No intraluminal thrombus was identified, although the delayed nature of the surgery cannot exclude its possible presence at initial imaging. Post-operatively, the patient was continued on aspirin. His post-operative course was without complication.

Discussion

Carotid Stenosis

Several large randomized clinical trials have shown the efficacy of carotid endarterectomy over medical therapy for significant carotid stenosis. Both the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [8] and the Asymptomatic

Atherosclerosis Study Committee (ACAS) [2] studies used digital subtraction angiography (DSA) to determine the degree of carotid stenosis. DSA involves a well-documented risk of complication not experienced with MRA, ultrasound, or CT angiography (CTA). Additionally, plaque morphology may contribute to the risk of stroke and, therefore, requires accurate assessment of the degree of vessel stenosis and the morphology of the occlusive lesion.

Risk of Catheter Angiography

Catheter angiography is associated with a well-documented risk of creating emboli from a plaque with potential resultant cerebrovascular accident. The ACAS reported a 1.2% risk of persisting neurologic deficit or death following DSA, whereas surgical risk was 1.5% [2]. NASCET reported a 0.7% risk of persistent neurologic deficit or death associated with selective angiography [8]. In contrast, neither MRA (TOF or gadolinium enhanced) nor ultrasound has been associated with any similar degree of complication. However, for noninvasive imaging modalities to supplant DSA in diagnosing carotid stenosis and ultimately in characterizing a lesion as surgical or nonsurgical, they must closely approximate DSA in accuracy.

Accuracy of Non-Invasive Methods

Multiple studies have evaluated the reliability of non-invasive methods in the determination of carotid artery disease [10].

A) MRA

Nederkoorn et al [6] compared the accuracy of noninvasive testing for carotid artery stenosis. Their study included 350 patients tested with ultrasound, MRA, and DSA between 1997 and 2000 in 3 centers. Their study points out the fact that there were significant advances in the field of MRA during their study period, including the introduction of contrast-enhanced (CE)-MRA. In their study, MRA was more sensitive in identifying stenosis >70%, but

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specificity was equal. They further report that both digital ultrasound and MRA have a tendency to overestimate the degree of stenosis. Although this has been reported in some studies [13], other reports do not confirm this [5].

Young and colleagues [14] studied 137 carotid arteries in 70 patients using DSA, duplex ultrasound, and TOF MRA on each patient. DSA was used as the gold standard for technique comparison. Results were more concordant in higher-grade stenosis than for mild stenosis. When identifying a surgical lesion, the number of disagreements between MRA and DSA (14 vessels) was nearly identical to the number produced by interobserver variability (13 vessels) in reading the DSA results. The authors suggest that when duplex ultrasound and MRA both classify a lesion as 70% or greater, the patient may be referred for carotid endarterectomy. If there is a disagreement between the two methods, DSA should be preferred.

Patel et al [9] also suggest that correlation between duplex ultrasound and MRA data would negate the need for DSA. They report that the sensitivity and specificity of classifying a surgical lesion using MRA alone are 93% and 83%, respectively, but increase to 97% and 92% when combining these 2 modalities. Of marked concern in their report is the low 22% sensitivity for TOF MRA to detect plaque ulceration clearly demonstrable on DSA. The authors recommend the use of both two-dimensional and 3D TOF MRA when using this modality to assess stenosis.

Johnson and colleagues [4] studied TOF MRA, CE-MRA, and Doppler ultrasound compared with catheter angiography in 40 patients. They determined that duplex ultrasound alone was not sufficiently sensitive, but MRA (3D TOF) could be used to assess stenosis accurately. Sensitivity for TOF MRA was 82%; specificity was 100% (95% CI 88-99%). Combining TOF and CE-MRA yielded a sensitivity of 100% and specificity of 95%; however,

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the authors did not believe that the routine use of CE-MRA was warranted. They suggested 3 situations in which the use of contrast was indicated: 1) when 3D TOF imaging demonstrates complete occlusion, CE MRA should be used to confirm this finding; 2) when patients are unable to remain still long enough to acquire 3D TOF imaging, CE-MRA is beneficial; and 3) when it is desirable to image the aortic arch and carotid bifurcation in the same acquisition.

Remonda et al [11] compared 3D CE-MRA with DSA in 120 patients. Grading of stenosis agreed in the two imaging modalities in 89% of the cases. Furthermore, the authors determined that CE-MRA agreed with DSA in 93% of the severe stenosis (70-99%) group in the study. All occlusions were accurately determined by CE-MRA, however, 2/9 pseudo-occlusions with very low flow were missed by CE-MRA as determined by DSA.

Nederkoorn et al [7] published a review of the literature comparing duplex ultrasound, MRA, and DSA. MRA again proved superior to duplex ultrasound and compared favorably with DSA. In this study, MRA had a pooled sensitivity of 95% and pooled specificity of 90% when used to diagnose critical stenosis (70-99%), compared with 86% and 87% for duplex ultrasound. When determining carotid artery occlusion, the pooled sensitivity and specificity for MRA were 98% and 100%, respectively. Duplex ultrasound is likely insufficient according to this study to be used as a single imaging modality in determining whether carotid artery stenosis meets surgical criteria.

Other studies suggest that CE-MRA may be sufficiently accurate for surgical determination. Friese et al [3] report that ultrasound and CE-MRA results were sufficient criteria for surgery in 93% of cases. In their series, 3 of 195 patients with high-grade stenosis on ultrasound went unrecognized by CE-MRA. The authors believe that current limitations in spatial resolution may prevent detection in cases of very short segment severe stenosis. This is

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the scenario in our second case; the patient had severe, very focal stenosis identified on DSA but missed with CE-MRA. In 19% of patients studied by Friese and colleagues, CE-MRA examinations were deemed of insufficient quality. The authors hypothesized that in thin patients with rapid circulation, venous contrast may interfere with arterial contrast, providing for reduced image quality [3]. They suggest that further improvements in post-processing of the data set, with the arterial and venous phases separated, may lead to better imaging results.

Back et al [1] have virtually eliminated the use of DSA in determining whether ICA stenosis meets surgical criteria. They do not use CE-MRA, citing quality degradation caused by venous overlap, instead opting for MRA with short repetition and echo times with venous signal suppression. They further suggest that DSA may be necessary in cases where near total ICA occlusion is present (>95%). The slow flow velocity present at such a lesion greatly reduces accuracy needed to determine length of stenosis in the diseased segment [1].

B) CTA

Randoux and colleagues [10] studied 44 carotid arteries in 22 patients using DSA, CTA, and gadolinium CE-MRA on all patients. The sensitivity and specificity of gadolinium-enhanced MRA were 93% and 100%, respectively, compared with DSA. The authors also determined that CE-MRA was highly effective in quantifying the length of the stenosed segment. CE-MRA did not appear to be as effective as CTA in determining plaque irregularities. This is likely due to the limitation of gadolinium-enhanced MRA regarding spatial resolution. The limits in spatial resolution determination can be reduced by decreasing the field of view (FOV) and section thickness. It is this limitation of FOV, however, that led Randoux et al [10] to comment that MRA is insufficient to determine luminal irregularities. This same study determined that CTA is the most accurate means to analyze plaque morphology. Plaque

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ulceration was most accurately determined via gadolinium-enhanced MRA, followed by CTA, although CTA did depict one ulcerated plaque not seen on MRA [4].

Sameshima et al [12] used 3D CTA to study carotid disease in 64 patients. Their findings indicate that this modality is superior to CE-MRA and even DSA when identifying intimal calcifications and ulcerative plaque morphology. The patient in our first case had an ulcerated and calcified plaque at surgery. It is possible that 3D CTA would have enabled us to better quantify the atheroma. Sameshima and colleagues [12] use ultrasound and MRA as a screening tool in their hospital, and 3D CTA is used to determine degree of stenosis and for pre- and post-surgical evaluation.

Conclusions

Non-invasive techniques are increasingly being used in the evaluation of carotid atherosclerotic disease. Our institution frequently uses digital ultrasound combined with MRA to assess carotid stenosis. In both cases reported, flowing blood and ulcerated plaque appeared nearly indistinguishable on TOF MRA imaging; however, expanding the examination to include the gadolinium contrast MRA or DSA demonstrated the lesions more accurately. The limitations for MRA in assessing stenosis in an ulcerated or calcified lesions has been well documented as described above. Recent advances in CT angiography techniques may make this the study of choice in determining degree of ICA stenosis and plaque morphology.

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Figure Legends

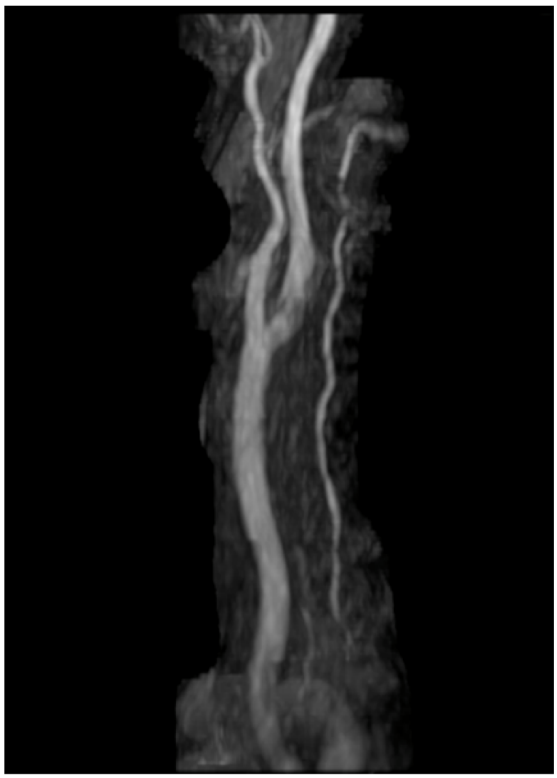

Figure 1: Magnetic resonance angiogram demonstrating no significant stenosis of the proximal right internal carotid artery.

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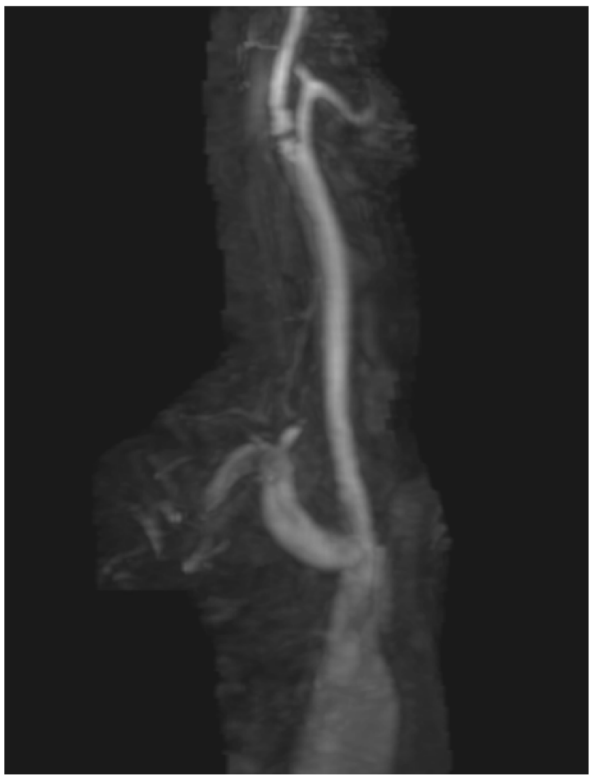

Figure 2: Three-dimensional time-of-flight magnetic resonance angiogram with gadolinium contrast shows significant stenosis of the proximal right internal carotid artery

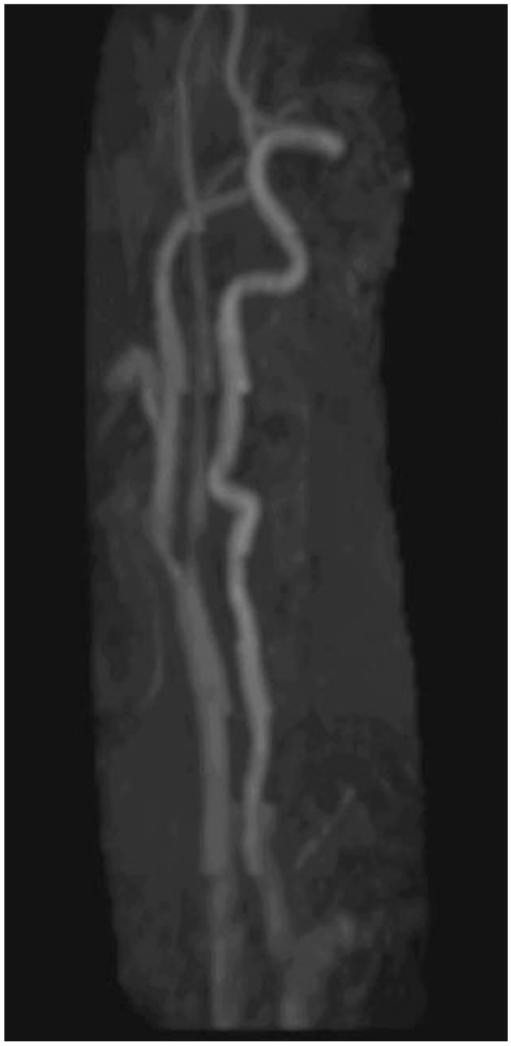

Figure 3: Magnetic resonance angiography shows moderate narrowing of the left internal carotid artery at its takeoff from the carotid bifurcation.

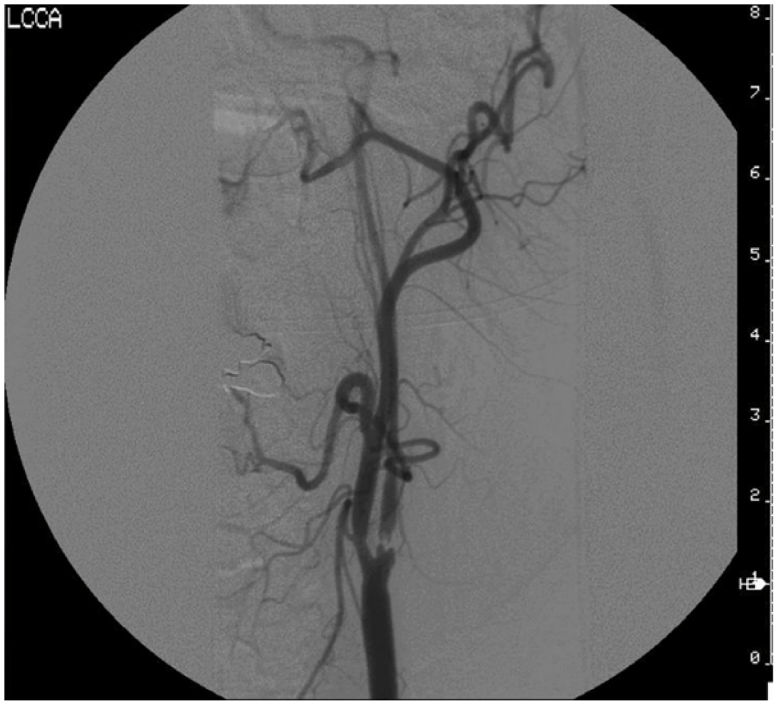

Figure 4: Cerebral catheter angiogram demonstrates severe narrowing of the proximal left internal carotid artery at its origin.