Multiple flow-related intracranial aneurysms in the setting of contralateral carotid occlusion: Coincidence or association?

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Abstract:
The prevalence of intracranial aneurysms (IAs) is higher in patients with internal carotid artery (ICA) stenosis, likely due to alterations in intracranial hemodynamics. Severe stenosis or occlusion of one ICA may result in increased demand and altered hemodynamics in the contralateral ICA, thus increasing the risk of contralateral IA formation. In this article, we discuss a relevant case and a comprehensive literature review as it pertains to the association of ICA stenosis and IA. Our patient was a 50-year-old female with a chronic asymptomatic right ICA occlusion who presented with diffuse subarachnoid hemorrhage. Emergent angiography revealed left-sided A1-A2 junction, paracilinoid, left middle cerebral artery (MCA) bifurcation, and left anterior temporal artery aneurysms. Brisk filling of the right anterior circulation through the anterior communicating artery was also identified, signifying increased demand on the left ICA circulation. Complete obliteration of all aneurysms was achieved with coil embolization and clipping. For our literature review, we searched the PubMed and EMBASE databases for case reports and case series, as well as references in previously published review articles that described patients with concurrent aneurysms and ICA stenosis. We selected articles that provided adequate information about the case presentations to compare aneurysm and patient characteristics. Our review revealed a higher number of patients with multiple aneurysms contralateral (25%) to rather than ipsilateral to (6%), the ICA stenosis. We discuss the pathogenesis and management of multiple flow-related IA in the context of the existing literature related to concurrent ICA stenosis and IA.

Keywords:
Carotid stenosis, endovascular, flow-related aneurysm, intracranial aneurysm, neurosurgery, subarachnoid hemorrhage

Introduction

Approximately 2.8% of the general population harbors an unruptured intracranial aneurysm (IA). IA rupture results in subarachnoid hemorrhage (SAH), which carries a 30-day mortality rate of 45% and moderate-to-severe neurologic disability in 30%–50% of survivors. The incidence of aneurysmal SAH ranges from 6 to 16/100,000 individuals depending on the country. IAs have also been shown to be associated with conditions that alter intracranial blood flow, such as arteriovenous malformations, collateral circulation from persistent fetal arteries, moyamoya disease and other vasculopathies, and atherosclerotic arterial stenosis or occlusion.

In this article, we present a patient with SAH who was found to have multiple left-sided anterior circulation IA and a chronic right ICA occlusion. We conducted...
a comprehensive literature review pertaining to the association of ICA stenosis and IA. The management of this complex clinical scenario is discussed, and the contribution of ICA stenosis-induced hemodynamic influences on IA formation is reviewed.

Case Report

A 50-year-old female with a past medical history significant for smoking, hypertension, and a chronic asymptomatic right ICA occlusion presented with a Hunt Hess grade III, Fisher grade III SAH [Figure 1a]. Angiography revealed a left 8 mm × 5 mm A1-A2 junction aneurysm, a 3 mm × 2 mm left paracallosal aneurysm, a 3 mm × 3.5 mm left middle cerebral artery (MCA) bifurcation aneurysm with an excrescence, and a 2.7 mm left anterior temporal artery aneurysm [Figure 1]. Brisk filling of the right anterior circulation through the anterior communicating (ACOM) artery was also identified, signifying increased demand on the left ICA circulation.

Due to the diffuse blood pattern, definitive confirmation of which aneurysm ruptured was not possible, however, the large size of the A1-A2 junction aneurysm and excrescence on the MCA bifurcation aneurysm made one of these the most likely culprit [Figure 2]. Complete obliteration of the A1-A2 junction, paracallosal, and MCA bifurcation aneurysms was achieved with coil embolization. The left anterior temporal aneurysm was left untreated in the acute setting due to its small size, regular shape, and low likelihood of being the ruptured aneurysm. The patient was unable to be weaned from an external ventricular drain and a ventriculoperitoneal shunt was ultimately placed. The patient was discharged neurologically intact on postbleed day 15 to an inpatient rehabilitation facility. The anterior temporal artery aneurysm was obliterated with clipping 6 weeks following the hemorrhage. Postoperative angiogram at that time demonstrated stable complete obliteration of the coiled aneurysms [Figures 3 and 4]. The patient made a complete recovery and is living independently. All aneurysms remained completely occluded on 8-month follow-up angiography.

Literature Review Methods and Results

For this report, we searched the PubMed and EMBASE databases for all case reports, case series, and references in previously published reviews regarding patients with concurrent aneurysms and ICA stenosis. To the best of our knowledge, we have included all available instances of coexistent IA and carotid artery stenosis in our analysis [Table 1].[10‑33] Because some of the individual patient records did not include all useful data (e.g., age and gender), the total number of patients is different for each category, and thus, the data are presented as percentages. In addition, aneurysm sizes that were presented as a range were not included in the calculations of means. The published cases of patients with multiple aneurysms all contralateral to the side of major ICA stenosis are presented in Table 2, and cases with multiple aneurysms all ipsilateral or bilateral to the side of major ICA stenosis are presented in Table 3.[10,12,13,18,20,24,25,29,30] In addition, we have collected the available data from case studies that only listed the average values for their cohorts instead of data from individual patients.[34‑40] These studies have not been compiled into a table because of insufficient data regarding the location of the aneurysms.

We found a total of 150 relevant patient reports in the literature. Of those, 134 (89.3%) had a single aneurysm and 16 (10.7%) had multiple aneurysms. Sixteen patients with multiple aneurysms had a total of 37 aneurysms: 12 patients had two aneurysms, three patients had three aneurysms, and one patient had

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**Figure 1:** (a) Noncontrast axial head computed tomography demonstrating diffuse subarachnoid hemorrhage. (b) Left internal carotid anteroposterior (AP) injection showing left-sided 8 mm × 5 mm A1-A2 junction aneurysm, 3 mm × 2 mm left paracallosal aneurysm, 3 mm × 3.5 mm middle cerebral artery bifurcation aneurysm with an excrescence, and a 2.7 mm left anterior temporal artery aneurysm (arrows). Note the large anterior communicating artery (ACOM), through which the right anterior circulation is supplied. (b and c) Left internal carotid AP injections demonstrate filling of the right anterior circulation through the ACOM complex.

**Figure 2:** Left anterior oblique injection better demonstrating the left middle cerebral artery bifurcation aneurysm with dome excrescence.
For both groups (a single aneurysm and multiple aneurysms), there were more female than male patients. Most of the aneurysms were located in the anterior cerebral circulation for patients with a single aneurysm (102/132, 77.2%) and for patients with multiple aneurysms (27/37, 73.0%). The most common aneurysm location for each group was the MCA and the second most common location for each group was the posterior communicating artery (PCOM).

Of the reports that listed laterality of both the aneurysm and the stenosis, most (72.6%) of the patients with a single aneurysm had IA ipsilateral to the ICA stenosis. Most patients with multiple aneurysms had aneurysms both ipsilateral and contralateral (69%) to the carotid stenosis; however, more patients (25%) had all of their aneurysms on the contralateral side than on the ipsilateral side (6%), as was the case with our patient. The proportion of patients that presented with symptoms attributed to the aneurysm (SAH, visual field defects, headache, paresis, and paresthesia) was higher for patients with multiple aneurysms (25.0%) than for patients with a single aneurysm (18.0%).

None of the patients with ICA stenosis and multiple aneurysms all contralateral to the side of major stenosis presented with aneurysm rupture. Of the four patients, only one was treated (clipping). No recurrence or rupture

Table 1: Statistical comparison of patients with single and multiple aneurysms from published individual cases

|                  | Single IA | Multiple IA |
|------------------|-----------|-------------|
| Patients, n (%)  | 134 (89.3)| 16 (10.7)   |
| Total number of aneurysms, n | 134 | 37 |
| Female (%)       | 54.1      | 30.0        |
| Age, mean (SD)   | 64.7 (9.9)| 64.5 (10.0)|
| Anterior circulation IA, % | 77.2 | 73.0% |
| Most common, location, n (%) | MCA (38, 28.4) | MCA (11, 29.7) |
| Second most common, location, n (%) | Pcomm (23, 17.1) | Pcomm (9, 24.3) |
| Largest IA in mm, mean (SD) | 5.9 (3.7) | 7.5 (4.8) |
| Second Largest IA in mm, mean (SD) | 4.0 (2.1) |
| Patients with All Contralateral IA* (%) | 27.4 | 25.0 |
| Patients with All Ipsilateral IA* (%) | 72.6 | 6.0 |
| Patients with Bilateral IA* (%) | 69.0 |
| Patients with Symptomatic IA (%) | 18.0 |
| Treated Symptomatic IA, % | 70.8 |
| Treated Symptomatic IA with aSAH, % | 4.4 |
| Treated Asymptomatic IA (%) | 29.6 |
| Treated Asymptomatic IA with aSAH (%) | 0.0 |
| Untreated aSAH** (%) | 3.5% (asymptomatic) | 10% (asymptomatic) |

*In relation to the side of major carotid stenosis, **aSAH found on follow-up studies in asymptomatic patients after initial imaging. CI: Confidence interval, MCA: Middle cerebral artery, Pcomm: Posterior communicating artery, SD: Standard deviation, IA: Intracranial aneurysm, aSAH: Aneurysmal subarachnoid hemorrhage
of the aneurysm was reported in that patient upon follow-up. Of the 12 patients with ICA stenosis and multiple aneurysms ipsilateral or bilateral to the side of major stenosis, three of them presented with SAH from a ruptured
aneurysm. Two of these patients initially presented with SAH and both patients were treated with aneurysm clipping. No follow-up data are available. The third patient did not initially present with rupture but suffered a fatal aneurysmal SAH 7 months after an initial presentation of left hemiparesis and the discovery of two unruptured IA that were left untreated. Of the 21 aneurysms in the nine other patients, six were clipped and one was coiled. For the cases with available data, none of these treated aneurysms showed the recurrence or rupture at follow-up.

A study by Kappelle et al. reported that nine out of ninety patients with ICA stenosis and concomitant IA had multiple aneurysms (10%), which is similar to our findings in the pooled literature data. They reported a slightly higher number of patients with ipsilateral aneurysms (56.6%) than patients with contralateral aneurysms (43.4%). However, because the data on the individual aneurysm locations is unavailable, we are unable to determine the number of patients with all ipsilateral and all contralateral aneurysms. A study conducted in South Korea by Cho et al. reported a high rate of patients with multiple aneurysms (29.1%) and more contralateral aneurysms (52.6%) than ipsilateral aneurysms, but they also did not report the laterality of all their patients’ aneurysms. In both of those studies and in four additional similar studies, there were no reported cases of SAH due to an untreated aneurysm in patients with single or multiple aneurysms.

**Discussion**

Our patient presented with multiple left-sided IAs and chronic asymptomatic right ICA occlusion. In comparison to the compiled data from the literature, she is 23 years younger than the average age of a patient presenting with multiple aneurysms (all contralateral) in the setting of carotid stenosis, possibly due to her risk factors of chronic hypertension and cigarette smoking. The only reported cases of aneurysmal SAH in patients with multiple aneurysms and coexistent ICA stenosis were of patients with ipsilateral aneurysms, making her case unique. Her MCA aneurysm matched with the most common location found in the data, whereas her paraclinoid and anterior temporal artery aneurysms were not as commonly found among other patients. Most patients in the literature with multiple aneurysms had IA both ipsilateral and contralateral (69%) to the ICA stenosis; however, more patients (25%) had all of their aneurysms on the contralateral side than on the ipsilateral side (6%), as was the case with our patient.

**Hemodynamic Stress and Aneurysm Genesis**

Initiation of IA development, growth, and eventual rupture is a complex process that is influenced by multiple genetic and environmental factors. Chronic hypertension, binge drinking, and cigarette smoking are all well-defined contributors to IA pathogenesis and the inflammatory cascade represents a potential common endpoint through which these environmental stimuli lead to IA genesis. Hemodynamic stress along vessel walls drives vascular remodeling, which is the end result of inflammation, endothelial dysfunction, and vascular smooth muscle cell (VSMC) phenotypic changes. Increased shear stress along a vessel wall is a known activator of the inflammatory response. IA most commonly form at vessel branch points, where hemodynamic stress is greatest. In addition, the strong link between IA and environmental stimuli known to disrupt vascular integrity (smoking and hypertension) highlights the contribution of abnormal blood flow and shear stress in IA formation. Endothelial cells, which serve as the interface between blood flow and the vessel wall, are key contributors to this process. The apical and basal surfaces of endothelial cells display multiple mechanical sensors, including, ion channels, integrins, cell adhesion molecules, and G protein-coupled receptors. These sensors respond to the mechanical stimuli of shear, stretch, and flow by altering their physical structure and initiating biologic signaling through mechanotransduction. VSMCs represent the primary cellular component of the tunica media and maintain vessel wall integrity. Under normal physiologic conditions, the cells remain in a nonmotile contractile state and allow the vessel wall to adapt to changes in blood pressure. In the setting of increased hemodynamic stress, the endothelium and VSMCs partake in complex and cyclical cascade of events that lead to disruption of the tunica media and extracellular matrix. VSMCs transition from the contractile phenotype to a secretory phenotype that is defined by gain in motility, a loss of markers of contractility, and expression of proinflammatory cytokines and matrix metalloproteinases. Histologic examination of IA walls, which demonstrates erratic migration and apoptosis of VSMCs, provides evidence of this phenotypic change. Aneurysm growth is defined by additional degradation of the tunica media and cellular loss. The walls of ruptured IA more frequently demonstrate hypocellular and hyalinized walls when compared to unruptured IA.

**Internal Carotid Artery Stenosis and Intracranial Aneurysm Formation**

Yang et al. reported a 6.3% prevalence of carotid stenosis and coexistent IA, which is more than twice the prevalence of incidentally found IA in the general population. This value includes IA both ipsilateral and contralateral to the ICA stenosis. Although the exact
mechanisms underlying IA formation in the setting of ICA stenosis have yet to be fully defined, it is postulated that hemodynamic changes in the intracranial vasculature heavily influence IA development. For IA ipsilateral to the stenosis, at least initially, autoregulation distal to the stenotic ICA likely leads to increased blood flow, increased blood flow velocity, and greater wall stress in the intracranial vasculature. As the stenosis progresses, flow to the intracranial circulation may decrease, or stop, in cases of complete occlusion. Examination of flow rate through a stenotic vessel has been demonstrated to remain stable, until the stenosis reaches 75%, at which point a significant reduction is observed. Severe ICA stenosis (75%–99%) results in a 35% reduction in blood flow through the artery, whereas occlusion also leads to a 14% flow reduction in the ipsilateral MCA. This may explain the reported higher number of patients with multiple contralateral aneurysms than with multiple ipsilateral aneurysms (5 to one including this case report). In addition, the eventual significant drop in flow through the stenosis likely also contributes to the finding that IA ipsilateral to ICA stenosis are of a mean smaller size than those IA located contralateral to ICA stenosis.

In those IA contralateral to the ICA stenosis, it is likely that the increased metabolic demand on the nonstenotic vessel increases blood flow, stretch, and hemodynamic stress distal to the nonstenotic vessel. Furthermore, these hemodynamic stresses are likely greatest at the sites of collateralization between the circulations (ACOM and PCOM). A recent quantitative magnetic resonance angiography study to assess hemodynamic changes that may lead to IA showed higher wall shear stress and flow velocity across vessels that provide collateral blood supply in the setting of ICA occlusion, namely the ACOM and PCOM. Additional studies have reported larger aneurysm sizes on the side contralateral to a stenotic ICA. Our patient presented with an asymptomatic chronic right ICA occlusion and a large ACOM through which the entire right anterior circulation was fed by the left ICA. The left A1-A2 junction was also the site of the patient’s largest aneurysm.

Our patient also had two IA arising from the left MCA, which we believe to be secondary to increased flow and hemodynamic stress through the parent vessel. Based on the downstream location of the MCA from the ICA, increased demand on the ICA contralateral to the stenosis is transmitted to the ipsilateral MCA and in turn, would translate into conditions conducive to MCA IA formation.

IA in the setting of concomitant posterior circulation artery occlusion are less common than aneurysms in the setting of anterior circulation occlusion for a number of reasons. First, in general, posterior circulation IA are significantly less common, accounting for only approximately 10%–15% of all IA. Second, occlusion of a single vertebral artery reduces the overall flow through the posterior circulation. Increased flow through the contralateral vertebral artery could result in conditions suitable for IA formation along that vessel; however, contrary to the intracranial ICA, there is only a single large caliber branch, the posterior inferior cerebellar artery (PICA). Overall PICA IA is rare, and there are multiple variations in its caliber, origin, and angioarchitecture. Finally, severe posterior circulation atherosclerosis and stenosis are associated with a higher mortality rate and may not allow adequate time for the chronic hemodynamic changes that lead to aneurysm formation.

One situation in which posterior circulation aneurysms are likely formed due to increased blood flow is moyamoya disease, where chronic anterior circulation occlusion leads to increased demand through the posterior circulation. A review of published cases demonstrated a higher incidence of posterior circulation aneurysms (50%–60%) in moyamoya patients than in the normal population.

Management Considerations in Our Patient

Our patient presented with a Hunt Hess grade III Fisher grade III SAH and was found to have multiple left-sided IA. Due to the diffuse blood pattern, identification of the ruptured IA was difficult; however, the large A1-A2 junction and MCA bifurcation aneurysm with an ex crescence were felt to be the most likely rupture source. The left anterior temporal and paracclinoid aneurysms were of a small size and regular shape.

The A1-A2 junction, MCA bifurcation, and paracclinoid aneurysms were all narrow-necked and suitable candidates for obliteration with either clipping or coiling. The left anterior temporal aneurysm was small, of wide-neck morphology, incorporated the M1 trunk and left anterior temporal artery, and was deemed a better candidate for clipping. Coiling was chosen for the A1-A2 junction, MCA bifurcation, and paracclinoid aneurysms for multiple reasons. First, the patient presented with a high-grade hemorrhage, hydrocephalus requiring an external ventricular drain, and significant cerebral edema. Endovascular treatment allowed for rapid occlusion of all three aneurysms without the need for extensive Sylvian fissure dissection and brain retraction. Second, the left-sided location of all the aneurysms would have forced dissection of the dominant left frontal and temporal lobes. Third, treatment of the paracclinoid aneurysm would have required a clinoectomy and neck dissection to gain proximal control of the left internal carotid artery. Temporary occlusion of the left
internal carotid artery would result in hypoperfusion of both hemispheres due to the occluded right ICA. Finally, the A1-A2 junction aneurysm was the largest and possibly the aneurysm most likely to have ruptured. In the event that temporary clipping of the left A1 segment would be required, the entire right hemisphere would be deprived of blood flow through the ACOM complex.

All aneurysms were obliterated, and the patient made a complete recovery, yet we do acknowledge that coiling of flow-related aneurysms could be subject to criticism. Although the literature tends to demonstrate improved clinical outcomes with coiling,[76,77] multiple studies have shown superior durability of clipping when compared to coiling.[78] In part, recurrence of coiled IA is caused by continuous blood flow compacting the coil mass within the dome.[79] Certainly, the exaggerated hemodynamic parameters that led to the formation of our patient’s IA, would likely contribute to an increased risk of recurrence. On short-term follow-up angiography, all aneurysms remain completely obliterated with no evidence of residual or recurrence. Follow-up angiography at 8 months showed persistent complete occlusion of all treated aneurysms. The patient will require routine long-term serial imaging to identify the potential recurrence.

The management of patients presenting with multiple IA in the setting of ICA stenosis should be considered on a case-by-case basis. As shown by our review of the literature, the risk of rupture in untreated patients is not greatly increased when the patient has more than one IA (3.5%; 10%). The difference can be explained by the larger mean size of aneurysms in our sample of patients with multiple aneurysms (5.9 mm and 7.5 mm), as larger IA carry a higher risk of rupture. Prophylactic management should likely depend on risk factors for aneurysmal rupture other than the number of aneurysms, such as size, age, morphology, and intracranial location.

Conclusion

We present a patient with a chronic asymptomatic right ICA occlusion and aneurysmal SAH, who was found to have multiple, likely flow-related, left-sided anterior circulation aneurysms. All aneurysms were obliterated with a combination of endovascular and microsurgical techniques, and the patient made a complete recovery. A review of published case reports/studies of patients with concurrent ICA stenosis and IA revealed a higher number of patients with multiple aneurysms contralateral (25%) to, rather than ipsilateral to (6%), the ICA stenosis. We discuss these findings in relation to the available data pertaining to hemodynamics and IA formation. Ruptured IA in the setting of concomitant significant ICA stenosis or occlusion represents a challenging clinical scenario that is further complicated by the presence of multiple IA. An understanding of IA pathogenesis, cerebral hemodynamics, and available treatment options are critical to successful patient management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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