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ACTA2 Mutation and Intracranial Saccular Aneurysm: Case Report and Review of Literature

CASE REPORT

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ABSTRACT

Background: ACTA2 encodes the smooth muscle alpha-actin protein, which serves a contractile role important to vessel structure and function. Mutations in ACTA2 are implicated in a variety of disease processes that are often systemic and may include intracranial aneurysms and arteriopathies. We support the implication of ACTA2 mutations in intracranial aneurysms and suggest that the underlying vessel anomalies may present unique dynamic properties.

Case Presentation: We present a 32-year-old male with a history of ACTA2 mutation diagnosed with bilateral fusiform dilatation of the internal carotid artery (ICA) and saccular aneurysm of the right ICA. He was scheduled for right ICA flow diversion, but the pre-surgical angiogram indicated improvement of the diameter and saccular morphology of the aneurysm, and no intervention was pursued.

Conclusions: This case raises the possibility that ACTA2-associated aneurysms may present with an unconventional disease course. Although additional studies are needed, physicians should consider the potential for interval changes in aneurysm morphology when monitoring similar patients with ACTA2 mutation.

KEYWORDS

alpha-actin, vascular smooth muscle cells, saccular aneurysm, genetic variant

BACKGROUND

Genes that encode the smooth muscle actin proteins are diverse and exhibit tissue-specific expression. The ACTA2 gene specifically encodes the alpha-actin protein found in vascular smooth muscle tissue, where it serves a contractile role.[1–4] ACTA2 is highly conserved across various species, indicating its importance to vessel function and vessel formation.[2,3] Genetic mutations of the ACTA2 gene have been implicated in various vascular diseases, including multisystem smooth muscle dysfunction syndrome (MSMDS), familial thoracic aortic aneurysm and dissection (FTAAD), patent ductus arteriosus (PDA), early onset stroke, coronary artery disease (CAD), cerebrovascular arteriopathies, and intracranial aneurysms.[3,5,6]

The pathologic presentations of ACTA2 mutations appear to coincide with specific genetic variants and exhibit variable expressivity among carriers of the mutation.[3] The inheritance pattern for ACTA2 mutations is recognized as autosomal dominant.[2] Among patients with symptomatic ACTA2 mutations, most present with systemic and aortic abnormalities and pathologies; thus, much of the literature is focused on understanding these disease presentations. There are relatively few patient case reports of cerebrovascular pathologies associated with ACTA2 and little understanding of the underlying pathophysiology.

We aim to characterize those ACTA2 mutation variants for which intracranial aneurysm and cerebrovascular pathologies are associated and provide a new report of intracranial saccular aneurysm in a patient with a confirmed ACTA2 mutation of an unknown variant. Additionally, we support consideration of cerebrovascular monitoring in patients with ACTA2 mutation given the apparent potential for fusiform aneurysms and spontaneous regression of ICA saccular aneurysms, as illustrated in this report.

CASE PRESENTATION

A 32-year-old male with a past medical history significant for a confirmed ACTA2 mutation (genetic variant unknown) and multiple ascending aortic aneurysms treated surgically with a Bentall procedure presented after an abnormal magnetic resonance angiography (MRA) study in the setting of headaches. His family history is significant for an ACTA2 mutation associated with familial dissection. Subsequent angiography demonstrated marked ectasia with fusiform aneurysmal dilatation of the bilateral internal carotid arteries (ICAs) and a Moyamoya-like vascular pattern intracranially (Figure 1). A 3-year follow-up angiogram demonstrated the development of a right-sided 1.4 cm saccular aneurysm in the cavernous segment of the ICA (Figure 2). He was planned for right ICA Pipeline flow diversion given the size and morphology of the aneurysm.

The results of the pre-surgical angiogram, performed to evaluate the status of the saccular and fusiform aneurysms of the ICAs, indicated

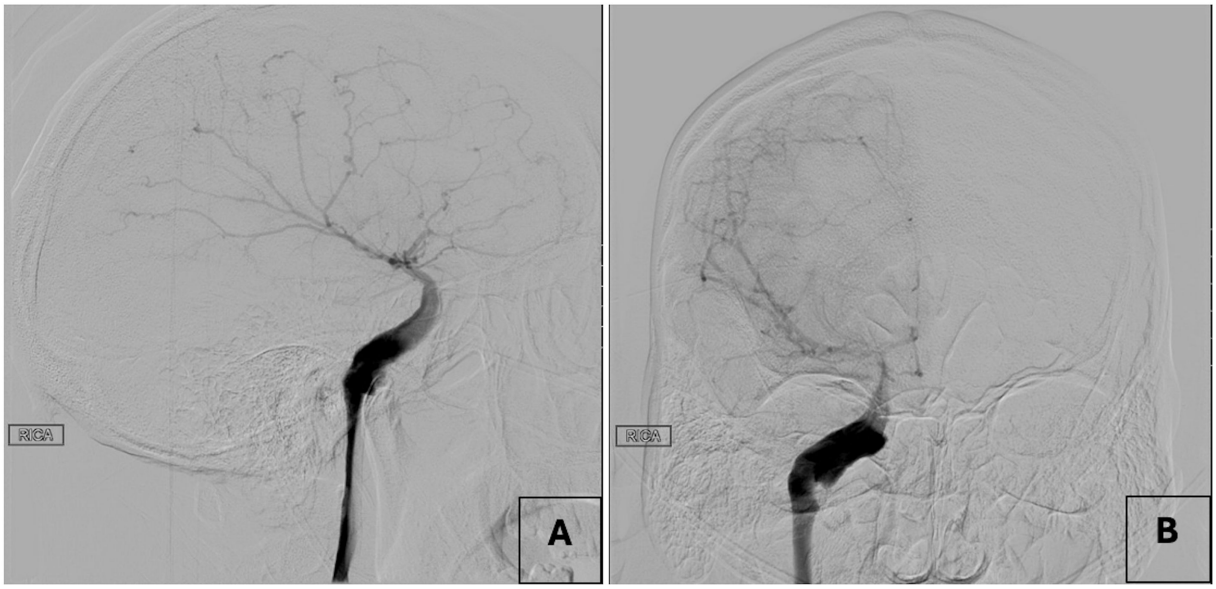

FIGURE 1. Initial angiogram demonstrating marked ectasia with fusiform aneurysmal dilatation of the right ICA: (A) lateral and (B) anteroposterior views.

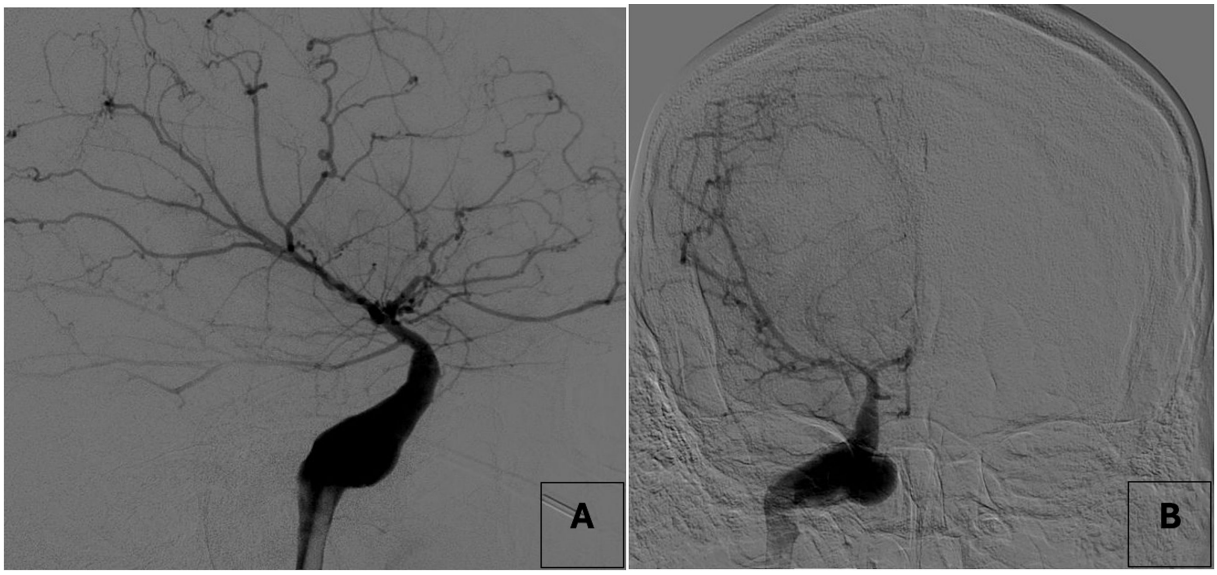

FIGURE 2. Follow-up angiogram of the right ICA: (A) lateral and (B) anteroposterior views.

spontaneous improvement of the saccular aneurysmal component (Figure 3). There was a 10-month delay between the diagnostic angiogram and the intervention due to patient hesitancy. The improvement of the saccular component obviated the need for surgical intervention. He was subsequently scheduled for follow-up with MRA in 2 years. Notably, long-term follow-up data are not presently available.

METHODS

A literature review was performed using PubMed with the following search terms: 'ACTA2 mutation', 'ACTA2 intracranial aneurysm', 'ACTA2 arteriopathy', 'ACTA2 cerebral aneurysm', and 'de novo ACTA2 mutations'. Additional articles were identified through a review of the reference lists of relevant publications. Abstracts were reviewed for relevance to ACTA2 mutation and intracranial vessel formation, function, or morphology. Articles focused on systemic disease, heart and great vessels disease, and lung disease were included only if they also provided relevant information on intracranial vessels in ACTA2 mutations. Articles that did not address ACTA2 mutation associated with intracranial vessel pathology and articles blocked by access limitations were excluded from the literature review.

CHARACTERIZING ACTA2 MUTATIONS

There are many documented ACTA2 mutations recognized as causes of disease, each associated with abnormalities in vessel wall formation and function. Some mutations are associated with intracranial arteriopathies, and within this subset are mutations associated with documented cases of intracranial aneurysms. The various intracranial manifestations of ACTA2 mutations are

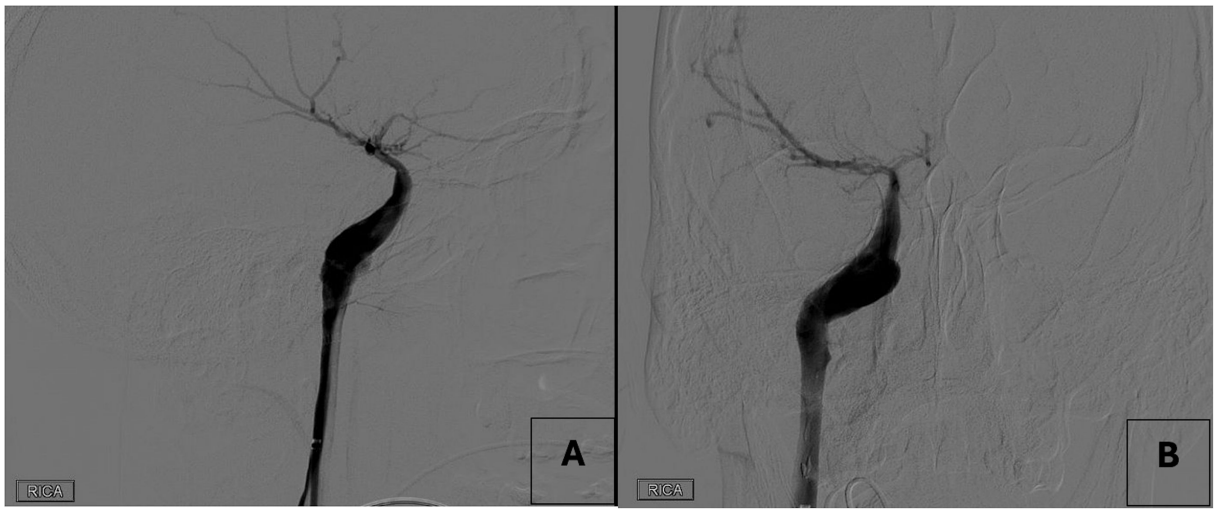

FIGURE 3. Pre-surgical angiogram of the right ICA: (A) lateral and (B) anteroposterior views.

TABLE 1. Reported ACTA2 variant-associated intracranial artery characteristics.

ACTA2 variant	Pathologic cranial vessel findings	Source
p.Arg179His	– Patulous dilatation of petrous ICA – Intracranial Moyamoya-like vascular pattern	[2]
	– Bilateral fusiform aneurysms of the internal carotid artery from the common carotid to the cavernous sinus – Linearization and stenosis of cerebral arteries with secondary corpus callosum deformity – Cerebral arteriopathy – Ischemic stroke	[7]
	– Dilatation of proximal carotid arteries – Diffuse occlusive arteriopathy of distal internal carotids and their branches – Linearized intracranial vasculature – Lack of lenticulostriate collaterals – Periventricular/deep white matter signal changes	[8]
	– Dilatation followed by stenosis of ICA in the cavernous or laceral segments – Intracranial Moyamoya-like vascular pattern	[9]
p.Arg179Cys	– Intracranial Moyamoya-like vascular pattern	[2]
	– Straightening of cerebral vessels – Potential for stroke	[10]
p.Arg179Leu	– Intracranial Moyamoya-like vascular pattern	[2]
	– Intracranial Moyamoya-like vascular pattern – Dilatation followed by stenosis of cavernous ICA	[9]
p.Arg179Ser	– Intracranial Moyamoya-like vascular pattern	[2]
p.Met46Arg	– Intracranial Moyamoya-like vascular pattern	[2]
p.Arg258Cys	– Intracranial Moyamoya-like vascular pattern	[2]
	– Intracranial Moyamoya-like vascular pattern	[11]
	– Supraclinoid carotid stenosis with dilated posterior communicating arteries providing compensatory flow – Lack of lenticulostriate collaterals – White matter lesions associated with vessel stenosis	[8]
p.Arg258His	– Intracranial Moyamoya-like vascular pattern	[2]
p.Asn117Lys	– Patulous dilatation of petrous ICA – Intracranial Moyamoya-like vascular pattern – Brain parenchymal anomalies – Lack of temporal artery tortuosity	[2]

described across case studies and literature reviews, providing a preliminary picture of the disease states seen with each ACTA2 variant (Table 1).

ACTA2 mutations identified in patients with intracranial vessel abnormalities include p.Arg179His, p.Arg179Cys, p.Arg179Leu, p.Arg179Ser, p.Met46Arg, p.Arg258Cys, p.Arg258His,

and p.Asn117Lys.[2] Among the documented ACTA2 variants, those involving the p.Arg179His mutation, the most common cause of MSMDS, appear to be the most common ACTA2 mutations associated with intracranial vessel abnormalities.[2,9] This includes aneurysms of the petrous ICA, Moyamoya-like patterning of the intracranial branches of the ICA, and white matter signal changes.[2,7,8] The Arg179 amino acid in alpha-actin appears to be implicated in other missense mutations leading to intracranial arteriopathy, with or without other systemic smooth muscle cell disorders.

DISCUSSION AND CONCLUSION

The potential for intracranial vessel abnormalities associated with ACTA2 mutations is generally recognized. The case we present raises the possibility that these changes in intracranial vessel anatomy are dynamic and may require alternative interventions and monitoring compared to more typical presentations of intracranial aneurysms.

Vascular smooth muscle pathology is a known factor in aneurysmal change. Intracranial saccular aneurysms have been shown to exhibit decreases in alpha-smooth muscle actin (alpha-actin) within the arterial media, like the decreased alpha-actin production seen in intimal smooth muscle cells of atherosclerotic plaques.[12] Given the implication of abnormal smooth muscle formation in saccular aneurysms, ACTA2 mutations may present a predisposition for aneurysm formation. However, this predisposition should be recognized as a distinct pathology from morphologically similar saccular aneurysms not associated with an ACTA2 mutation, since there is an apparent transience as noted in this case.

Although the ACTA2 variant for this case is unknown, the literature recognizes the p.Arg179His mutation as a major cause of systemic vascular disease, including intracranial arteriopathies and aneurysms. Arginine and histidine are implicated in different enzymatic functions and protein-folding conformations.[13] This offers a basis for the pathophysiologic process occurring at the level of the alpha-actin protein, although the mechanisms underlying possible protein dysfunction and different cerebrovascular phenotypes remain poorly understood. Prentice et al. (2022) hypothesize that ACTA2 mutations present with unique intracranial aneurysm morphology due to neural crest cell migration patterns giving rise to vascular smooth muscle cells, like the localized stenoses seen in aortic coarctation. Vascular smooth muscle cells of the head and neck develop from cephalic neural crest cells and may explain the fusiform dilatations and stenosis seen in the petrous and supraclinoid segments of the ICA, respectively, which may classify ACTA2 mutations with this phenotype as neurocristopathies.[2] While these proposed mechanistic contributors to the pathophysiology are promising, the literature lacks strong data to suggest causality between the mutation and the phenotype or the mutation and neural crest cell dysfunction.

The presented findings of this case are significant in that the saccular component of the patient's aneurysm improved without the need for flow diversion within 10 months. It is unclear if this spontaneous resolution is directly related to the pathophysiology of the patient's ACTA2 phenotype, but it cannot be ruled out. We speculate that distinct vessel morphology and remaining contractile functions of alpha-actin may play a role in spontaneous resolution of saccular aneurysms. Further investigation of vessel wall structure and function in vessels with an ACTA2 mutation would be needed to more clearly define the causal mechanism(s).

The lack of variant-specific data in this case limits our ability to suggest a clear association between a specific ACTA2 variant and the observed phenotype; however, it adds to the repertoire of observed intracranial vessel morphologies and dynamics associated with an ACTA2 mutation. This case should be recognized as a novel report of an ACTA2 mutation associated with intracranial vessel aneurysm dynamicity but cautiously considered given the lack of evidence to suggest causality between the mutation and the observed aneurysm dynamics.

Ultimately, the initially indicated procedure for saccular aneurysm exclusion was not performed on the patient given the pre-surgical angiogram findings. In patients with ICA saccular aneurysm and confirmed ACTA2 mutation, repeat vascular imaging prior to intervention may be considered to assess for interval changes in aneurysm morphology. Patients with ACTA2 mutations should be counseled regarding the potential for atypical cerebrovascular manifestations and the importance of longitudinal follow-up. Additional studies are needed to determine optimal monitoring and treatment strategies for these patients.

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Patient consent

Informed consent was obtained from the patient for the publication of this case report and review.

Disclosures

The authors declare no conflicts of interest related to this research, study, or project. They have no personal or financial relationships that could influence their work.

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