Progressive Aortic Dilation Associated With *ACTA2* Mutations Presenting in Infancy

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abstract

Mutations in the gene *ACTA2* are a recognized cause of aortic aneurysms with aortic dissection in adulthood. Recently, a specific mutation (Arg179His) in this gene has been associated with multisystem smooth muscle dysfunction presenting in childhood. We describe 3 patients with an R179H mutation, all of whom presented with an aneurysmal patent ductus arteriosus. Detailed information on the rate of aortic disease progression throughout childhood is provided. Death or need for ascending aortic replacement occurred in all patients. Genetic testing for *ACTA2* mutations should be considered in all infants presenting with ductal aneurysms.

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The *ACTA2* gene encodes the smooth muscle α2-actin protein. Pathogenic mutations within *ACTA2* result in disrupted contractility and are a recognized cause of aortic dissection that typically presents in adulthood.[1] Recently, the Arg179His mutation has been associated with a severe phenotype with highly variable manifestations appearing in infancy.[2] This pediatric form of the disease, known as multisystemic smooth muscle dysfunction syndrome, affects smooth muscle in the eyes, lungs, gastrointestinal tract, genitourinary tract, central nervous system, and cardiovascular system.[2,3] Although vascular disease has been well described in adults with other *ACTA2* mutations, no data are available on the progression of vascular involvement in patients with the diffuse smooth muscle form of the disease. We report on 3 patients with an Arg179His mutation in *ACTA2*, further delineating the clinical manifestations of this newly reported disease (Table 1), and provide a detailed review of the progression of vascular involvement.

CASE 1

A female term infant presented at 1 month of age with a febrile illness complicated by a seizure. A computed tomography (CT) scan of the head was normal. A murmur was noted and echocardiography revealed a "giant" patent ductus arteriosus (PDA), a secundum atrial septal defect, coarctation, and pulmonary hypertension. At age 2 months she underwent PDA ligation and surgical resection of the coarctation. By 1 year of age, pulmonary hypertension had resolved. At 18 months she was diagnosed with intestinal malrotation with volvulus requiring surgical intervention. At age 2 years she was referred to neurology for evaluation of transient spasticity in her lower extremities and bilateral congenital mydriasis. MRI showed diffuse white matter changes of unclear etiology. At age 3 years she presented with transient inability to use her right arm or leg. MRI showed more extensive white matter abnormalities. The patient's symptoms of hemiparesis completely resolved. At age 6 years the patient was found to have grade III vesicoureteral reflux and bladder dysfunction requiring ureteral reimplantation. Intermittent seizures persisted, and at age 6 years cerebral

TABLE 1 Clinical Features of Multisystem Smooth Muscle Dysfunction Syndrome

Variable	Patient 1	Patient 2	Patient 3	Other Cases Previously Described in the Literature[2–10] (N = 23)
Age at presentation	1 month	Birth	1 month	Prenatal to 25 years
Age at death	NA	11 months	NA	2, 3, 11, and 17 years[a]
Age at report	15 years	Deceased	31 years	11–26 years
Reason for presentation	Aneurysmal PDA, seizure	Aneurysmal PDA, umbilical varix	Aneurysmal PDA	Dilated pupils, aneurysmal PDA, stroke, seizures, limb ischemia
Age at diagnosis of aortopathy	22 months	2 months	7 years	24 months to adulthood
Age at genetic diagnosis	14 years	5 months	26 years	Childhood to adulthood
Clinical features				
Umbilical varix	+	+	−	One previous case described[3]
Congenital mydriasis	+	+	+	Noted in all previous patients
Retinal vessel tortuosity	+	+	+	Noted to be age-dependent
Other aneurysms	Transverse aortic arch	PDA	Transverse arch, descending thoracic aorta, abdominal aorta	Diffuse; more distal disease described at older ages
Other vascular anomalies	Aberrant RSCA	External iliac artery occlusion		Retinal artery occlusion, brachial artery occlusion, femoral artery occlusion, distal CNS vessel occlusion
Pulmonary hypertension	+	+	+	Noted in 6 previous patients
Lung disease	−	+	+	Noted in 13 previous patients
Cardiac	Coarctation, ASD, dilated pulmonary arteries, aberrant RSCA,	ASD/dilated pulmonary arteries	Isthmus narrowing, ASD/dilated pulmonary arteries	Coarctation in 1 patient,[2] aortic valve dysplasia in 1 patient[7]
Gastrointestinal	Malrotation, volvulus with or without obstruction	Malrotation/volvulus/obstruction	Chronic constipation	Noted in 7 previous cases
GU	VCUR s/p ureter reimplantation	Incomplete bladder emptying	Vesicoureteral reflux	Urinary abnormalities described in 16 previous cases, including megacystitis with prune belly in 2 previous cases[4,10]
Cerebrovascular	Moyamoya disease	Diffuse aneurysmal dilation of the right ICA from petrous through supraclinoid segments	Beaded appearance of vessels with aneurysmal dilation and narrowing	Clinical stroke noted in 13 previous patients with presentation from neonatal period to adulthood
CNS	Cerebellar tonsillar ectopia; periventricular white matter abnormalities	Periventricular white matter abnormalities	Periventricular white matter abnormalities	White matter abnormalities described in all patients evaluated with the exception of a 3-month-old infant; Chiari malformation, abnormal lobulation of the frontal lobes

ASD, atrial septal defect; CNS, central nervous system; GU, genitourinary; PDA, patent ductus arteriosus; RSCA, right subclavian artery; s/p, status post; VCUR, vesicoureteral reflux; +, present; −, absent.

[a] Previous deaths occurred in a 2-year-old from fulminant liver failure, a 3-year-old from PDA rupture, an 11-year-old from unknown causes (autopsy not revealing), and a 17-year-old after aortic dissection.[2–4]

angiography revealed moderate narrowing of the cavernous and supraclinoid portions of the right internal carotid artery with narrowing extending into the anterior and middle cerebral arteries as well as aneurysmal dilation of the base of the left internal carotid artery with moderate narrowing distally. Tortuosity of distal vessels was noted. Surgical cerebral revascularization was performed. On routine cardiology follow-up the patient was noted to have progressive ascending aortic dilation (Table 2) and subsequent dilation of the aortic arch. The patient was maintained on low-dose atenolol and subsequently low-dose enalapril, neither of which was titrated upward due to a low normal blood pressure and concern regarding preservation of cerebral perfusion in the face of vascular narrowing. At age 13 years, after publication of the first patient series of *ACTA2* R179H mutations,[2] genetic testing was performed and revealed a de novo heterozygous *ACTA2* mutation (R179H). The patient was referred for surgical intervention for a valve-sparing ascending aortic and hemi-arch replacement. At 1 year postoperatively the patient remains well with no evidence of distal aortic aneurysms on CT scan.

CASE 2

A female infant presented in utero at 25 weeks' gestation with a large umbilical varix without associated hydrops. Induction was performed at 38 weeks due to a progressive increase in the size of the varix. At birth, the infant was cyanotic with respiratory distress and hypotension requiring ventilator and inotropic support. Echocardiogram revealed normal biventricular function, a small atrial secundum defect, pulmonary hypertension, and an aneurysmal PDA with right to left shunting. Inhaled nitric oxide was started. Abdominal ultrasound showed intestinal malrotation with volvulus for which the patient underwent a Ladd procedure and detorsion of the bowel, which was complicated by protracted postoperative ileus. The patient was eventually able to tolerate nasojejunal continuous feedings with only intermittent vomiting but was never able to tolerate bolus gastric feeds. An upper gastrointestinal series revealed poor bowel motility without anatomic obstruction. On day 54 of life the patient underwent PDA ligation. On inspection, the ductus was aneurysmal and friable and cardiopulmonary bypass was required for ligation. Complete closure could not be obtained, and a small residual shunt persisted. Postoperatively, the patient was noted to have bilateral congenital mydriasis. CT imaging of the head revealed no acute pathology. An *ACTA2* mutation was suspected in light of the pupillary abnormality and aneurysmal PDA. Genetic testing confirmed a de novo Arg179His *ACTA2* mutation. Pulmonary hypertension persisted in the setting of a moderate residual PDA, and at 14 weeks of age cardiac catheterization was performed and the ductus device occluded. Chest CT at age 6 months showed areas of air-trapping and thickened irregular septa throughout both lungs. From 4 months onward, the patient was only able to be extubated for brief periods of time, and at 10 months of age she underwent tracheostomy. Despite adequate ventilation and medical treatment of pulmonary hypertension including sildenafil, with subsequent addition of bosentan and then iloprost, she developed right-heart dysfunction and died of a pulmonary hypertensive crisis at 11 months. Progressive aortic dilation was noted on serial echocardiography (Table 2). The patient was normotensive and no antihypertensive therapies were initiated throughout her clinical course.

TABLE 2 Serial Aortic Diameters and Indexed Dimensions (*z* Scores)

Age	Aortic Root		Ascending Aorta	
	Diameter, mm	*z* Score	Diameter, mm	z Score
Patient 1				
2 years	19.2	+3.4	21.1	+6.0
6 years	22.5	+3.8	27.8	+8.3
7 years	25.6	+4.0	29.4	+8.1
8 years	26.0	+4.4	33.0	+9.4
11 years	34.4	+6.7	38.7	+9.6
12 years	35.0	+6.4	39.7	+11.2
13 years	38.0	+8.0	44.0	+12.0
Patient 2				
2 days	8.6	−0.4	9.7	+1.5
6 weeks	10.8	+0.2	13.0	+3.3
12 weeks	11.0	+0.4	14.3	+3.9
7 months	14.6	+2.2	16.5	+4.5
11 months	16.0	+3.0	18.0	+6.0
Patient 3				
7 years	40.0	+10.4	36.0	+8.1
10 years	48.0	+11.5	38.0	+7.6
11 years	50.0	+11.5	40.0	+7.7
11.5 years	55.0	+13.4	40.0	+7.5
12 years	59.0	+14.0	42.0	+7.5

CASE 3

A female neonate presented with a murmur and was noted to have an aneurysmal PDA and pulmonary hypertension. She underwent ductal ligation at age 4 months. Because of its size, the PDA could not be completely occluded and a small shunt remained. Repeat cardiac catheterization at age 8 months showed resolving pulmonary

hypertension. The patient was lost to follow-up until age 7 years at which time a new murmur was noted, and an echocardiogram revealed aneurysmal dilation of the ascending aorta and proximal aortic arch with aortic insufficiency. Serial echocardiography showed progressive aortic dilation (Table 2). At age 11 years, the patient underwent an attempt at a valve-sparing root replacement. The valve was abnormal on inspection with nodular thickened leaflet tips. Because of significant aortic insufficiency, a Bentall procedure and hemi-arch replacement were ultimately performed. The isthmus was noted to be relatively hypoplastic but was of normal size for age and was thus not addressed. At the time of surgery, the right pleural space was entered and the right lung was noted to be covered with multiple macroscopic blebs. Over the course of follow-up, the patient developed recurrent transient neurologic symptoms consistent with transient ischemic attacks in addition to a stroke. Cerebral imaging revealed diffuse fusiform dilation of both common and internal petrous carotid arteries, multiple areas of focal narrowing and dilation with a "beaded" appearance in the anterior and posterior circulation, and encephalomalacia in the right anterior cerebral artery territory associated with diffuse decreased caliber of the right anterior cerebral artery. Diffuse white matter changes were present. Other medical problems included vesicoureteral reflux and bladder hypotonia. The patient underwent genetic testing, which revealed a de novo R179H *ACTA2* mutation and was included in the original manuscript of this disease, therein described as patient E.[2] Serial aortic imaging over the 18 years after surgery showed progressive dilation of the transverse aortic arch to a maximal diameter of 46 mm, progressive dilation of the brachiocephalic artery and left subclavian artery, and development of aneurysms of the descending thoracic aorta and the abdominal aorta and its branches (Fig 1). Twenty-four-hour ambulatory blood pressure monitoring revealed normal recordings without evidence of hypo- or hypertension on low-dose atenolol therapy. Atenolol dosing could not be titrated beyond 0.5 mg/kg per day due to significant fatigue. At 20 years out from the original ascending aortic replacement, the patient remains well but with progressive distal aortic aneurysmal disease.

DISCUSSION

After the first description in 2010 of 5 children with Arg179His *ACTA2* mutations, there have been continued publications of newly diagnosed patients. There are now a total of 25 patients, including those described herein, with multisystemic smooth muscle dysfunction syndrome. Previous publications have highlighted the multisystemic clinical manifestations at presentation (Table 1).[4,6,7] There is, however, an absence of publications describing the natural history of one of the most lethal components of the disease, namely progressive aortic dilation.

In this series, we describe 2 previously unreported patients with an *ACTA2* Arg179His mutation that resulted in multisystemic smooth muscle dysfunction. We document the presence of progressive aortic dilation beginning in childhood in 3 affected patients. Although previous reports on other *ACTA2* mutations have noted no aortic dilation in affected children,[11] few data exist on the prevalence and rate of progression of aortic aneurysmal disease in association with this specific Arg179His mutation. Two reports of aortic dilation and/or aortic dissection in childhood exist,[2,5] but the presence and severity of aortic aneurysmal disease in childhood overall remain unknown. Our data suggest that aortic dilation begins shortly after birth and progresses relatively rapidly during childhood. Close surveillance with echocardiographic or alternate imaging appears to be warranted. The role of medical therapy in prevention of progressive aortic dilation in this disease is unknown. Given the unclear role of losartan or atenolol therapy in children with other aortopathies,[12] and the fact that this disease includes areas of both vascular narrowing as well as dilation, it appears premature to advocate universal medical therapy in these patients. Abnormalities of the aortic valve and aortic coarctation, which have been noted in single instances previously,[2,7] were also noted in 2 of our patients and may be additional manifestations of the condition for which the patient should be assessed. Because these patients typically present with an

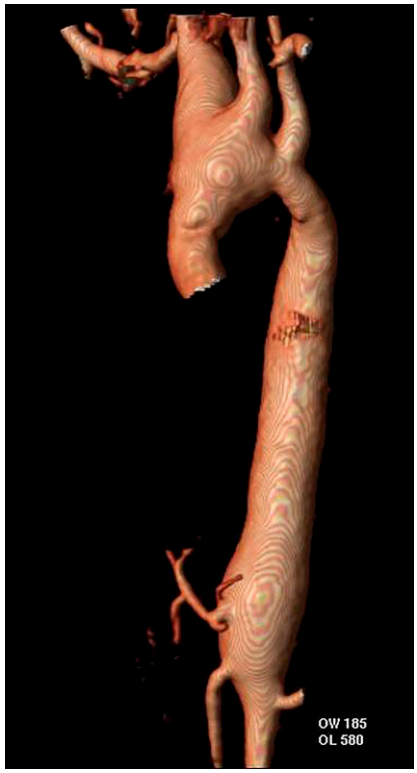

FIGURE 1
CT scan of the thoraco-abdominal aorta in patient 3 performed 18 years after aortic valve and root replacement. The image shows aneurysmal dilation of the aortic arch, innominate artery, descending thoracic aorta, and abdominal aorta.

aneurysmal PDA in childhood, early consideration of the condition on the part of the cardiologist is essential. Genetics referral, testing for *ACTA2* mutations, and ongoing cardiac follow-up with frequent imaging of the aortic root and ascending aorta are recommended.

ABBREVIATIONS

CT: computed tomography
PDA: patent ductus arteriosus

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