

Arterial tortuosity syndrome: A rare inherited form of connective tissue disorder with SLR2A10 gene mutation

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Introduction

Arterial tortuosity syndrome (ATS) is an extremely rare autosomal recessively inherited connective tissue disorder characterized by elongation, twisting, stenosis and aneurysm formation of large and medium size arteries¹. The phenotype also includes characteristic facial features, skeletal involvement, skin laxity, hernias, intestinal and genitourinary involvement². Histological findings, including disruption of elastic fibres of the media and fragmentation of the internal elastic membrane of large and medium size arteries have been described².

ATS is caused by homozygous mutations in SLC2A10 gene which is autosomal recessively inherited and located in the long arm (q) of chromosome 20 (20q13.1)². The gene encodes GLUT 10, a facilitated glucose transporter. GLUT 10 is expressed in mitochondria and endoplasmic reticulum membranes and may act by scavenging of free radicals in mitochondria and collagen maturation in the endoplasmic reticulum but the mechanism of its deficiency in causing the histological changes or the arterial vascular anomalies is not known. ATS can lead to life-threatening vascular complications such as rupture, dissection and ischaemic insult due to blockage of blood supply to vital organs and was considered a potentially fatal condition in early infancy¹. Current evidence suggests that the occurrence of complications is variable and less severe^{2,6}. Life expectancy is longer and the prevalence of sudden vascular events are rare in adolescence

or in adults² than previously described. ATS does not show gender predilection². The prevalence or incidence is unknown². Approximately 100 cases have been reported so far across the world².

Case report

The proband is a two year ten-month-old boy, the 3rd child of healthy non-consanguineous parents born following uneventful pregnancy and delivery. His growth and psychomotor development were age appropriate. An incidental cardiac murmur was detected following admission to a local hospital with a lower respiratory tract infection and he was subsequently referred to the Lady Ridgeway Hospital for specialised cardiology evaluation.

He had an uncomplicated neonatal period and infancy. There was no known family history of sudden cardiac death or vascular disease. On clinical examination, he was noted to have mid-facial hypoplasia, blepharophimosis, down slanting palpebral fissures and Harrison's sulci.

His initial echocardiographic evaluation revealed a dilated aortic root, main pulmonary artery (MPA) with proximal branch pulmonary artery (BPA) stenosis and Grade 2 aortic regurgitation.

Cardiac catheterization was performed to visualize the aortic and pulmonary vasculature (Figures 1-6).

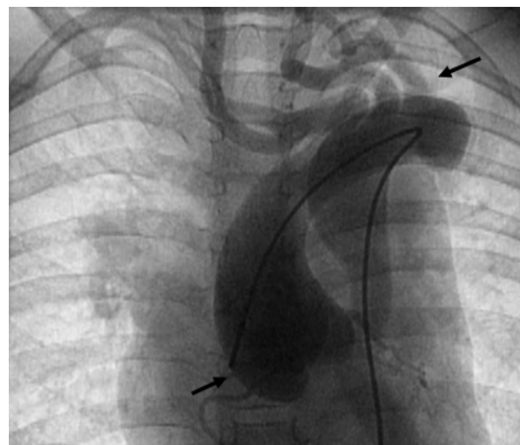


Figure 1: Aortic angiogram showing a dilated aortic root (arrowed), and tortuosity of main head and neck vessels

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Figure 2: Descending aortic angiogram showing aneurysmal dilatation (arrowed) and tortuosity

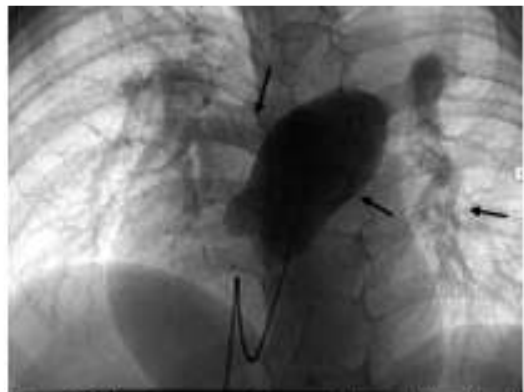


Figure 3: Main pulmonary artery angiogram with grossly dilated main pulmonary artery, stenosis of branch pulmonary artery and tortuosity of lobar arteries (arrowed)



Figure 4: Aortic arch angiogram showing elongated aortic arch (arrowed) and extensive tortuosity brachiocephalic vessels



Figure 5: Descending aortic angiogram showing tortuosity of mesenteric and renal vessels (arrowed)

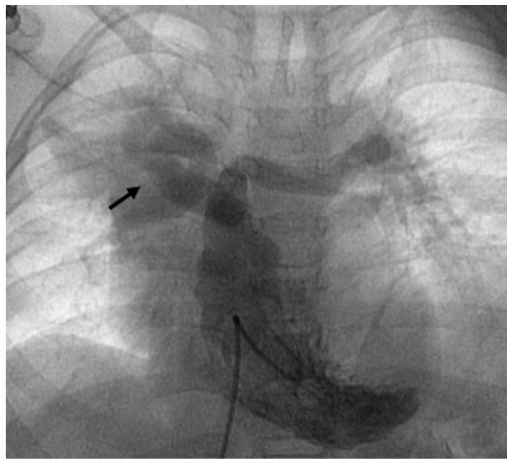


Figure 6: Main pulmonary artery angiogram depicting the dilated main pulmonary artery and tortuosity of branch pulmonary arteries of sister

Aortic angiogram revealed a dilated aortic root, left sided elongated and tortuous aortic arch and brachiocephalic vessels (Figures 1 and 4). The descending thoracic aorta demonstrated aneurysmal dilatation. The abdominal aorta, mesenteric and renal arteries also showed evidence of tortuosity (Figures 2 and 6). Pulmonary angiogram showed dilated MPA with bilateral proximal BPA stenosis. The lobar and segmental pulmonary arteries also illustrate abnormal tortuosity (Figures 3 and 5).

His six-year-old sister had a history of hiatal hernia in the neonatal period for which she had surgery during the first week of life. On examination, she showed facial similarities to her bother with mild skin laxity and hypermobile joints. Her echocardiogram showed dilated pulmonary arteries and dilated aortic root. Aortic and pulmonary angiograms were performed to delineate anatomy of the arterial system (Figures 4, 5 and 6) and

confirmed the echocardiogram findings. Ophthalmological examination was normal. Mutation testing was performed using genomic DNA extracted from blood in a specialised laboratory using previously described methods⁷. This confirmed a homozygous SLC2A10 gene in both affected siblings but not their unaffected carrier parents. Another sibling was neither clinically affected nor proven to share the gene mutations.

Discussion

ATS is an extremely rare autosomal recessively inherited multisystem, connective tissue disorder with characteristic vascular involvement¹. The disease can manifest in the neonatal period^{1,3}. The described features of ATS include characteristic long face, hypertelorism, blepharophimosis, long philtrum, down slanting palpebral fissures, micrognathia and beaked nose and they tend to look older than their age^{1,2}. Keratoconus is seen less commonly².

Skin manifestations include soft, doughy skin, hyper-extensibility of the skin but no increased bruisability. The bone and skeletal manifestations are arachnodactyly, high arched palate, pectus carinatum, joint contractures and joint laxity. The cardiovascular manifestations are the main cause of mortality⁶. The cardiovascular manifestations include ventricular hypertrophy, hypertension, pulmonary artery stenosis, aortic stenosis, arterial tortuosity and elongated arteries (large and medium-sized arteries including aorta)³. Further, hugely dilated aortic root and ascending aorta, tortuosity of arch, dilated MPA with proximal stenosis of BPA were described⁴. Tortuosity of the aorta or large arteries were invariably present⁵. The heterozygous carriers do not show arterial tortuosity or other phenotypic characteristics⁵. ATS is also associated with hernia including hiatal, diaphragmatic, sliding and gastric hernia³. In addition, diverticulitis, bowel necrosis due to thrombosis, ischaemic stroke, mental retardation and hypotonia are also described in association with ATS and these manifestations are less common². Although the symptoms of ATS are well defined, many details of this syndrome are not fully established due to rarity of the disease and lack of large clinical studies².

Both our patients showed most of the common phenotypic features. They did not have diverticulitis, keratoconus, hypotonia or mental retardation. Our patients are now 13 years old and 9 years old and do not have any vascular emergencies. The occurrence of sudden life-threatening vascular complications beyond infancy and early childhood is similar to the general population². Parents and the eldest sister were

screened with history, clinical examination and echocardiography but showed no phenotypic features of ATS. The diagnosis of ATS is based on clinical evaluation directed at identification of characteristic symptoms and signs². The specialised investigations helpful in the diagnosis of ATS are echocardiography, magnetic resonance angiography (MRA) and computed tomography (CT)². All these imaging modalities are useful in establishing the vascular phenotypic features of the disease^{2,3}. However, the confirmation of ATS is based on the demonstration of SLC2A10 gene mutation². Twenty-five mutations are described up to now including missense substitutions, nonsense nucleotide changes and deletions⁶. Both our patients had SLC2A10 gene mutation due to deletions.

Phenotype of ATS shows significant overlap with other syndromes and connective tissue disorders like Loeys-Dietz syndrome, Ehlers-Danlos syndrome, Marfan syndrome and autosomal recessive cutis laxa type 1^{2,6}. Each of these conditions should be considered in differential diagnosis⁶. The management of ATS is multidisciplinary and includes treatment of manifestations, surveillance, lifestyle modifications and genetic counselling for individuals who are at risk^{2,6}. Treatment is with beta blockers, angiotensin converting enzymes (ACE) inhibitors and angiotensin II receptor blockers to reduce the haemodynamic stress on vessel wall and hence reduce the risk of sudden vascular events⁶. The treatment should be cautious and the effectiveness is not established⁶. Localised aneurysms and stenosis are treated surgically⁶. Hernias need mesh repair as it can reoccur even following the primary repair⁶. Ophthalmology and orthopaedic complications need specialised management⁶.

ATS patients need routine follow up for cardiovascular manifestations including hypertension, pulmonary hypertension and ventricular dysfunction with echocardiograms and angiograms performed at regular intervals^{2,6}. In addition, affected individuals need regular pulmonology, ophthalmology, orthopaedic and orthodontic evaluations^{2,6}. Affected individual should not engage in contact sports, competitive sports or isometric exercises⁶. They should avoid routine use of decongestants, tobacco and sunbathing⁶. Genetic counselling is recommended to siblings and high-risk relatives of affected individuals^{2,6}.

SLC2A10 gene encodes GLUT10². GLUT10 is a protein with 541 amino acids and a member of the class III facilitative glucose transporter family². However, the exact molecular pathophysiology of how defective GLUT10 causes ATS is not fully

described yet^{2,6}. The SLR2A10 lies within the 20q12-13 region which linked to Type 11 diabetes mellitus⁶. Current evidence does not indicate increased susceptibility to overt diabetes mellitus in ATS^{5,6}. Our patient's glucose tolerance was normal.

ATS was first described by Ertrugal in 1967⁶. In ATS the clinical manifestation and presentation is diverse due to its multisystem involvement and vascular manifestations². Early identification is very important considering the limited treatment options, surveillance for manifestations and complications, family counselling and genetic counselling^{1,2,5}. The pregnancy related issues of this rare entity are not yet described⁶. Umbilical and hiatal and inguinal hernias, cutis laxa and unexplained respiratory distress in the neonatal period are common and need cardiovascular evaluation in view of early identification of this rare entity^{2,5,6}.

The severe vascular complications include early aggressive aortic root aneurysms, neonatal intracranial bleeding, ischaemic stroke and gastric perforation⁶. No reports document vascular dissections or ruptures among the existing literature beyond the neonatal period^{2,6}. The clinical spectrum of this rare vascular disease warrants diagnostic workup for infantile respiratory distress syndrome (IRDS), hernias (umbilical, hiatal, inguinal and diaphragmatic) and cutis laxa⁵. ATS children need close monitoring of the aortic root early in life, and extensive vascular imaging afterwards^{2,6}.

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