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Multidisciplinary Management of ATS in a Pediatric Patient: a case report

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Case Report

Keywords: Arterial Tortuosity Syndrome, pediatric vascular disease, SLC2A10 mutation, vascular tortuosity, respiratory distress, congenital vascular anomalies, failure to thrive, GLUT10 deficiency, connective tissue disorder

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11087114/v1

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Additional Declarations: No competing interests reported.

Abstract

Arterial Tortuosity Syndrome (ATS) is a rare autosomal recessive connective tissue disorder caused by biallelic pathogenic variants in the SLC2A10 gene, resulting in dysfunction of the GLUT10 transporter. It is characterized by elongation and tortuosity of large- and medium-sized arteries, with possible aneurysm formation and stenosis, and may be associated with substantial morbidity and mortality during early childhood due to cardiopulmonary complications. We report the case of a 14-month-old Jordanian male who presented to the emergency department with recurrent respiratory distress, failure to thrive, and cyanotic episodes, requiring urgent admission to the pediatric intensive care unit because of bilateral pneumonia and gastroenteritis. Physical examination revealed multiple connective tissue and dysmorphic features, including hypotonia, hernia, hyperextensible skin, talipes equinovarus, and blue sclera. Genetic testing identified a homozygous frameshift variant in SLC2A10 (c.56dup; p.(Leu20Profs*6)), establishing the diagnosis of ATS. Imaging and echocardiographic studies additionally demonstrated cardiopulmonary involvement consistent with the syndrome, necessitating multidisciplinary evaluation and management involving cardiology, pulmonology, and cardiothoracic surgery. This case demonstrates the phenotypic heterogeneity and diagnostic complexity of ATS. Although cardiovascular abnormalities are considered hallmark manifestations, recurrent respiratory distress and failure to thrive were prominent features in our patient, highlighting that substantial pulmonary morbidity may be an important component of the early clinical presentation. Molecular genetic testing is particularly valuable for distinguishing ATS from other connective tissue disorders with overlapping phenotypic features. Early recognition is essential because delayed diagnosis may result in clinical deterioration and missed opportunities for appropriate cardiovascular and pulmonary surveillance. This case emphasizes the importance of considering ATS in infants presenting with connective tissue features accompanied by recurrent respiratory manifestations and supports early genetic testing, multidisciplinary care, timely intervention, and appropriate surveillance to improve clinical outcomes.

Background

ATS is a rare X-linked genetic disorder associated with some birth defects (1,2). IT was described as a very severe disease with a high mortality rate because of its major cardiovascular malformations (1). Both females and males are at the same risk of developing it, although one study suggested a higher male prevalence (3,4). The main leading reason for the ATS is inactivation of glucose transporter 10 (GLUT10) receptors due to mutations in the SLC2A10 gene encoding the 541-amoni-acid leading to defects in collagen and/or elastin. The GLUT10 transporter belongs to the SLC2A10 family and facilitates the uptake of D-galactose, 2-deoxy-D-glucose, D-glucose, and dehydroascorbic acid (1,5). This reduces hydroxylation of prolyl and lysyl residues, leading to weakness of large and medium-sized arteries. It's believed that the weakness happened due to upregulation of transforming growth factor- β (TGFβ) signaling pathway and genes responsible for vascular smooth muscle relaxation, extracellular matrix proteins, and copper transport (1,6). Studies of large-vessel biopsies found that elastic fibers were distorted and disintegrated in vascular tissues (7). Remarkably, this tortuosity makes disruptions in

the blood circulation and increase shearing stress of the vessel wall, leading to atherosclerosis and cardiovascular stroke potentiality. It also results in loss of vascular stiffness, which may lead to chronic hypertension, vascular dissection, or aneurysm formation (1,8). A molecular genetic test should be performed to distinguish ATS from other connective tissue diseases (CTDs), as it shares some dysmorphic features with them, such as Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndrome (EDS). This helps design appropriate targeted follow-up and timely interventional treatment or cardiovascular surgeries when needed. Signs similar to those of other CTDs include soft, velvety, or hyperextensible skin; hypermobile joints; abdominal hernias; cutis laxa; skeletal anomalies; keratoconus; and congenital contractures. It also shares some dysmorphic facial features (such as an elongated face, micro/retrognathia, a cleft palate and/or bifid uvula, and hypertelorism) (1,3). Its arterial tortuosity is also similar to that seen in fibromuscular dysplasia (FMD) and spontaneous coronary artery dissection (SCAD) (3). Children during infancy usually present with dyspnea and cyanosis due to involvement of the pulmonary arteries. Several patients died at a young age, mainly because of cardiopulmonary complications (1). Our unique case report talks about a young child who presented to the ER with pneumonia and was diagnosed with ATS syndrome after doing genetic test to diagnose his dysmorphic features.

Case Presentation

A case of a 14-month-old Jordanian male admitted to the pediatric intensive care unit (ICU) after suffering from bilateral pneumonia, poor feeding, gastroenteritis, and failure to thrive. His medical history included difficulties in feeding for a long time, inadequate weight gain since birth, and multiple episodes of cyanosis during feeding and crying. Immunizations are up to date. His family history does not include congenital diseases or consanguinity. During physical examination, the patient appeared ill, hypoactive, febrile, and mildly dehydrated with oxygen saturation at 88% on room air. He was underweight and malnourished because of poor feeding. Additionally, tachypnea, flaring nostrils, a congested throat, intercostal retractions, a barrel-shaped chest, diminished breath sounds, and cyanosis of the face (lips) and fingertips, with normal cardiovascular examination, were noted, indicative of compromised respiratory function. The patient was diagnosed with ATS before being admitted to the hospital. The patient's genetic test result showed a homozygous, presumed loss-of-function variant in the SLC2A10 gene (Fig. 1). He has never been hospitalized or diagnosed with any congenital abnormalities before. His symptoms were deteriorating, leading to an emergency hospitalization.

During physical examination, there was no heart murmur, regular rhythm and normal S1 and S2 heart sounds. The abdomen was soft and distended, suspecting organomegaly with no palpable masses. The patient was alert but lethargic, accompanied by age-appropriate reflexes, signifying a concerning clinical picture and indicating an underlying pathology. The remainder of the physical examination showed abnormal cheek morphology, blue sclerae, excessive wrinkling of palmar skin, hernia, hypotonia, premature skin wrinkling, and talipes equinovarus(Fig. 2). After admission, the patient underwent a comprehensive diagnostic evaluation to elucidate the etiology of the presenting symptoms. ECHO, abdominal US, and chest and pelvic X-rays were also ordered.

In addition, imaging studies, including a chest X-ray, supported the diagnosis of ATS. The X-ray revealed a partially situated within the abdominal cavity, alongside a defect in the lower sternum. An abnormal cardiac position caused cardiac displacement, evidenced by an enlarged cardiac silhouette and a mediastinal shift. Importantly, the X-ray indicates the presence of pulmonary edema but no pleural effusion (Fig. 3). Echocardiograph finds blood flow, valves, aortic and pulmonic vessels to be normal with the exception of anomalous venous drainage from the thorax and abdomen, a small patent foramen ovale (PFO), and a small ventricular septal defect (VSD); thus, supporting the diagnosis of ATS.

Given the complexity of the ATS, several consultations were held to ensure adequate management. The needs of the syndrome were referred to cardiology for management: routine echocardiography and oxygen therapy. Potential surgical interventions were evaluated by the cardiothoracic surgery team, as pulmonology provided support for the patient's hypoxic respiratory status with continuous oxygen therapy and monitoring of pulmonary function (Table 2).

Table 2
Consultations.

Specialty	Reason for Consultation
Cardiology	Management of ATS; echocardiography
Cardiothoracic Surgery	Evaluation for potential surgical interventions
Pulmonology	Management of hypoxic respiratory status

The pulmonary team management plan was to stabilize the patient on continuous-flow low-oxygen therapy to maintain his oxygen saturation above 92%. His vital signs and respiratory status were monitored regularly to closely follow the patient’s progress. ATS is usually associated with severe anatomical malformations with poor pulmonary function, which leads to recurrent respiratory distress and failure to thrive, and requires a multidisciplinary approach to management.

After patient stabilization, discharge planning began with outpatient follow-up with pediatric cardiology and surgical teams to discuss potential surgical interventions once the patient could tolerate them. The nature of the ATS and the anticipated long-term prognosis were also discussed with the family. This case highlights how complex congenital anomalies can be and the necessity of multidisciplinary team involvement to treat patients appropriately.

Discussion

ATS is a rare autosomal recessive genetic condition described first in 1967, present usually during childhood and characterized by elongation, aneurysm, stenosis, and tortuosity of the major arteries due to disruption of elastic fibers in the arterial wall, specifically the medial layer (1,9). A 14-month-old Jordanian male presented with signs of respiratory distress and failure to thrive, along with an SLC2A10 gene mutation, adding new findings about ATS to the existing literature research. He presented to the ER

with rapid breathing, bluish skin, and using his accessory muscle demonstrating impaired breathing. The pathway of oxygenation is obstructed by the vascular malformations that naturally occur in ATS patients, and this patient has mild tracheomalacia. Although the patient was not previously diagnosed with congenital anomalies or hospitalized, his clinical manifestation showed multiple connective tissue manifestations, such as hypotonia, talipes equinovarus, hernia, lax skin, and dysmorphic facial features. The imaging studies done during his admission in the PICU demonstrated abnormal cardiac positioning and pulmonary edema, while the echocardiography revealed minor intracardiac defects and anomalous venous drainage. Laboratory genetic testing for this patient revealed a new SLC2A10 gene mutation called c.56dup p. (Leu20Profs*6) which had not been documented before. Although all the SLC1A10 gene mutations are associated with GLUT10 function loss, its pathogenesis role in ATS is still controversial. GLUT10 is the recognized DHA transporter, and in ATS, reducing its activity might lead to structural abnormalities in arterial wall proteins such as elastin and collagen due to oxidative stress or reduced hydroxylated prolines. Loss of SLC2A10 function activates the TGF-β signaling pathway (1). The degree of arterial tortuosity is increased by elevated TGF-β activity (10,6). There are three patterns of vascular tortuosity: type I forms a C or S shape in long vessels due to high-amplitude, low-frequency tortuosity. Type II is medium-amplitude-medium-frequency. Type III usually appears as tight coils and is characterized by low-amplitude, high-frequency tortuosity (11). Experimental and clinical studies found a strong association between vessel tortuosity and mechanical factors like blood flow, blood pressure, wall structural changes, and axial tension (12). A study reported that 90% of tortuosity occurs in the aorta and medium-sized arteries, and 48% of these cases affect the head, neck, and pulmonary arteries (4). Also, it was found to be 57% associated with pulmonary artery stenosis (1,13). Other characteristics of ATS are similar to those of CTDs, such as MFS, LDS, and EDS, including hypermobile joints and hyperextensible skin, as well as diaphragmatic and inguinal hernias (14,15,16). In addition, other skeletal features such as arachnodactyly, pectus carinatum, pectus excavatum, scoliosis, elbow/knee contractures, and campatodactyly. Ultrastructural and histopathologic investigations of skin and other tissue biopsies revealed disorganization of the connective tissue bundles in both the skin and the small arteries. This disorganization of collagen fibers and reduced level of elastin are the major causes of lax skin phenotype in ATS patients (3, 7, 17–19). Major ATS complications that led to a 40% mortality rate in patients under 5 years include cardiovascular system, respiratory insufficiency, or ventricular hypertrophy leading to heart failure and ischemic events or organ infarction (4,20). In contrast to the common presentation of the ATS, this case highlights its heterogeneity and shows that significant respiratory morbidity may occur even in the absence of severe structural cardiovascular abnormalities early in life.

Conclusion

ATS is a rare autosomal recessive disease that is closely associated with the cardiovascular and respiratory systems and usually presents in early childhood. Our case about a 14-month-old child presented to the ER with recurrent respiratory compromise and failure to thrive symptoms, with other dysmorphic features. It underscored the importance of considering ATS in the differential diagnosis when patients present with cardiopulmonary symptoms and connective tissue manifestations. We

cannot distinguish ATS from other CTDs until a genetic test shows a homozygous mutation in the SLC2A10 gene. Increasing awareness about ATS helps with early intervention, thus reducing mortality and morbidity in patients.

Declarations

Ethics approval:

Our institution does not require ethical approval for reporting individual cases or case series.

Consent to participate:

Written informed consent to participate in the study was obtained from the child’s parent

Consent for publication:

Written informed consent was obtained from the patient's parent for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in Chief of this journal

Competing intersts

We declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author’s contributions

All authors contributed significantly to the clinical management, data collection, drafting, and revision of this manuscript. All authors approved the final version for submission.

Funding:

All of us received no financial support for the research, authorship, and/or publication of this article.

Author Contribution

KA-S and ZH contributed to the conception and design of the case report. FQ, MA-S, and MA contributed to the collection and interpretation of clinical data and relevant literature. AK contributed to the clinical management and surgical aspects of the case. AZ contributed to the literature review, manuscript drafting, and critical revision of the manuscript. All authors contributed to the interpretation of the findings, critically reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Acknowledgement

AcknowledgementsThe authors confirm that no third-party editorial assistance was received for the preparation or submission of this manuscript. This submission was made by Dr. Ali Zarour on behalf of all co-authors. All authors have reviewed and approved the final manuscript and have authorized the submission

Availability of Data and Materials:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Figures

SEQUENCE VARIANTS

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES **	TYPE AND CLASSIFICATION ***
SLC2A10	NM_030777.4:c.56dup	p.(Leu20Profs*6)	N/A	Homozygous	PolyPhen: N/A Align-GVDG: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: Conservation_aa:	gnomAD: - ESP: - 1000 G: - CentoMD: -	Frameshift Likely pathogenic (class 2)

Variant annotation based on CentoCloud Bioinformatics pipeline. * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

Figure 1

*SLC2A10, c.56dup p.(Leu20Profs6): The SLC2A10 variant **c.56dup p.(Leu20Profs6)** causes a frameshift starting at codon 20 in exon 2 (of 5). This variant is predicted to escape nonsense-mediated decay but to remove more than 10% of the protein. It is classified as likely pathogenic based on CENTOGENE's implementation of the ACMG/AMP/ClinGen SVI guidelines. Also, ClinVar lists this variant as "likely pathogenic" (Variation ID: 2572073).*



Figure 2

Anonymized clinical photographs showing talipes equinovarus with excessive plantar skin wrinkling, consistent with the connective tissue manifestations of arterial tortuosity syndrome.

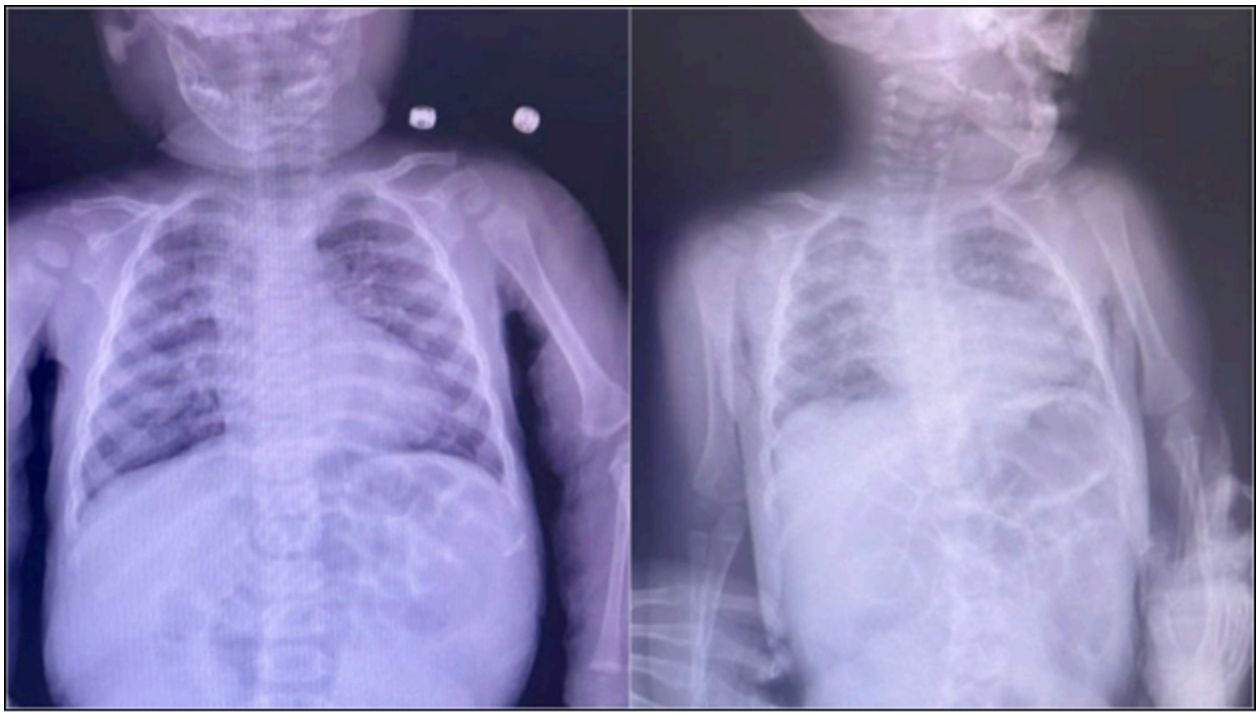


Figure 3

The X-ray photos reveal lung hyperinflation, characterized by flattened diaphragms and increased lung volume. Additionally, the X-ray shows increased interstitial markings, indicating pulmonary edema or other lung pathology, along with an enlarged cardiac silhouette and mediastinal shift.

Supplementary Files

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