Sonographic prenatal diagnosis of congenital Marfan syndrome

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Abstract:

Congenital Marfan syndrome is a rare and severe disease of the newborn, causing devastating and often fatal effects on the cardiovascular, pulmonary, and musculoskeletal systems. Familial mutations of FBN1 have been studied and identified in Marfan syndrome, but the congenital variant is often due to de novo mutations, limiting the diagnostic capabilities of genetic screening. Ultrasound is essential for early diagnosis and management, yet few cases of sonographic diagnosis have been cited in the literature. This report outlines one such case of congenital Marfan syndrome diagnosed at 24-week ultrasound. Further detailed reports should aim to improve screening, diagnosis, and treatment of congenital Marfan syndrome to advance options in family planning and disease management.

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Introduction

Marfan syndrome (MFS) is a disease of the connective tissue caused by a mutation of the FBN1 gene, and involves the integument, cardiac, ocular, and the pulmonary systems. Among the most common presenting symptoms are bilateral ectopia lentis, myopia, bone overgrowth, disproportionately long limbs (dolichostenomelia), scoliosis, spontaneous pneumothorax, and numerous heart defects. The greatest contributors to disease morbidity and mortality are cardiac anomalies including aortic root dilation, aortic dissection, and valvular prolapse.

Diagnosis of MFS is largely dependent on clinical identification of a spectrum of phenotypic presentations. Most MFS cases are not diagnosed until adolescence due to the late presentation of the characteristic features and lack of earlier screening tools. Diagnostic tools include the Gent revised criterion and molecular genetic testing for FBN1 mutation to verify. One exception allowing for earlier diagnosis of MFS is amniocentesis and CVS for screening of familial MFS. However, this screening is only available in cases with a pre-identified disease-causing allele. Even with an allele isolated, the testing gives no indication of disease spectrum and severity, as MFS has significant clinical heterogeneity and variability. Additionally, the most severe form of the disease is the neonatal variant, which is most commonly caused by a spontaneous de novo mutation.

Congenital MFS is an extremely rare and more severe disease variant. Physical presentation includes elongated stature, flexion contractures, characteristic facial dysmorphology, and

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severe progressive cardiac disease. Neonates often face intractable congestive heart failure and die within the first 2 years of life. Early identification is essential in management, yet difficult as most are a result of spontaneous de novo mutations. The diversity of de novo mutations is beyond prenatal genetic testing at this point, placing extra weight on the diagnostic capability of ultrasound in unsuspecting parents. Early sonographic diagnosis of this lethal condition is essential for perinatal management and family counseling. Perinatal management requires a pediatric cardiologist, NICU availability, and palliative care representation. Benefits of early diagnosis to the family include provision of genetic counseling, preventative management of carriers, and reassurance of unaffected relatives. As diagnostics improve and more outcomes are documented, ultrasound may guide choices regarding termination. Additionally, new treatment options may be available as the disease pathogenesis is better understood. Currently TGF-beta has a major role and in mice models, losartan has been proven effective in the primary prevention of progressive aortic root dilation.

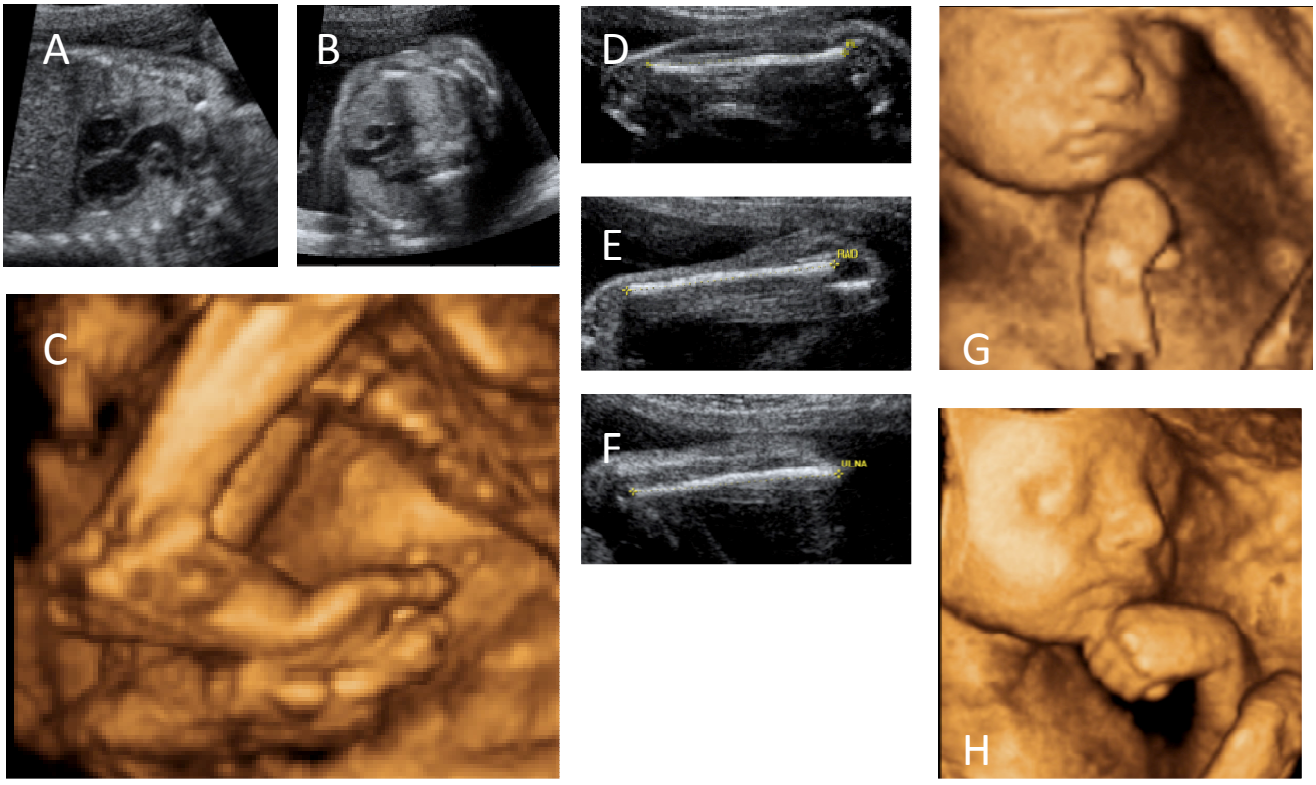

Figure 1: 24w4d Ultrasound

A: Left Ventricular Outflow Tract: no abnormalities of valvular roots noted at 24w4d, but appeared on following ultrasound at 28w4d. B: RV Outflow Tract. C: Arachnodactyly D: Right Femoral Length >95% E: Right Radial Length >95% F: Right Ulnar Length >95%. G/H: Fist clenching with thumb extending laterally

Case Report:

Prenatal Course

A 19-year-old G1P0 female presented for an initial OB visit at 22 4/7 weeks based on LMP. Initial ultrasound dated gestational age at 24w0d, with a 2-3 week discrepancy between long bone and abdominal circumference measurements, with femur and humerus lengths above 95th percentile. Patient was then seen in High Risk Clinic with an ultrasound dating the pregnancy at 24w4d with the following abnormal findings: long bone measurements above 95%, clenched fists, arachnodactyly, and subjectively high-normal amniotic fluid volume.

Follow-up ultrasound dated 28w4d demonstrated post valvular dilation of the left and right ventricular outflow tracts, as well as persistence of previous findings of fetal long bones and feet length greater than the 95th percentile, thumb extending beyond lateral border of hand when clenched in a fist. The fetal heart evaluation raised further concerns for possible congenital Marfan syndrome.

Ultrasound at 37w5d showed AFI of 6.79; assessment for fetal anomalies was not done at this time. Fetal evaluation prior to delivery at 38w5d identified oligohydramnios (AFI-4.92), persistence of elongated long bones, and a reassuring biophysical profile with a BPP 8/8. Fetal echo revealed dilation of the aortic root, proximal pulmonary artery, and pulmonary valve annulus.

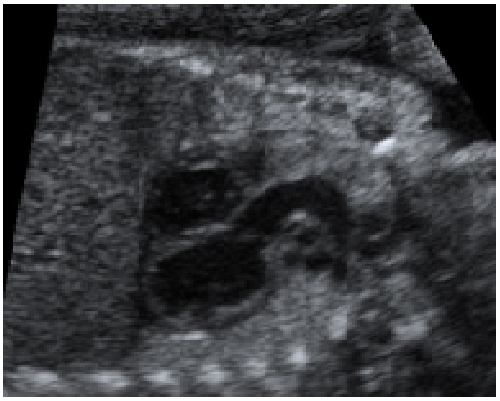

Figure 2: Dilated aortic root evident at 28w4d

Delivery

Patient was induced due to severe oligohydramnios at 38.5 weeks with support of the NICU and pediatric cardiology. Baby was a 3.01 kg (11-25%) female with Apgar scores of 8 and 9 at one and five minutes. Head circumference measured 32.5 cm (4-10%), and length measured 53 cm (76-90%). During labor, the fetus has persistent tachycardia (initial HR 190). Postnatal physical exam was significant for micrognathia, pectus excavatum, respiratory difficulty, and many additional findings consistent with MFS, including flexion contractures of all limb joints, wasting of leg muscles, arachnodactyly, and elongated extremities. Grade IV/VI systolic murmur was heard throughout with palpable thrill. Echocardiogram revealed aortic root dilation and mild insufficiency. Both sinuses of Valsalva and the supra-aortic ridge measurements plot above the 95% for BSA on the Roman Graphs. Additionally noted on echo was dysplastic mitral and tricuspid valves with moderate insufficiency, pulmonary valve insufficiency, and dilation of both atria and the left ventricle. A moderate sized PFO was noted with a left to right shunt, as well as small VSD with

restrictive left to right shunt. Infant was hypertensive with systolic blood pressures in the 90's-110's. MRA of neck showed abnormally elongated and tortuous carotid arteries, consistent with underlying collagen disease. Osseous survey revealed S-shaped thoracolumbar scoliosis. Ophthalmologic exam showed mid-peripheral iris with prominent transillumination defects and no ectopia lentis. Diaphragmatic paralysis was evident on ultrasound and fluoroscopy. Bronchoscopy revealed laryngomalacia and tracheobronchomalacia.

Immediately after birth, the infant experienced respiratory distress which required intubation and positive airway pressures. Despite continuing full NICU support, the baby had worsening respiratory distress, poor systemic perfusion, and a severe mixed acidosis. Pneumothorax was identified and showed no improvement with three thoracocentesis. At 35 days of life, parents requested withdrawal of support and the patient died shortly after.

Genetic Analysis

A three-generation pedigree was obtained. There is no known family history of Marfan syndrome or sudden death. Chromosome analysis and chromosomal microarray were both normal. FBN1 gene sequencing found a heterozygous IVS25T→A transversion. This change has not been previously reported as either a mutation or a polymorphism. Findings were consistent with a disease-causing mutation.

Literature Review and Discussion

Based on our survey of the literature in PUBMED (1950 to present), this is only the seventh case of congenital Marfan syndrome detected prenatally and confirmed on post-natal evaluation. Most recently was in 2007, with elongated femur noted at 22 weeks and cardiomegaly at 32 weeks. The other four cases were diagnosed in utero with findings of cardiomegaly, atrioventricular valve insufficiency and dilatation of the outflow tracts. These were detected at 29, 33, 34 and 37 weeks. Of these five previous cases, one pregnancy was terminated, one fetus died in utero and three died as neonates (Table 1). Retrospective reviews state the earliest possible sonographic findings to raise suspicion for MFS are femur length >95% at 22 weeks.[6] No previous studies have elaborated on the presence of abnormal feet and hand posturing en utero, nor utilized 4d sonographic capabilities to capture the images as we have noted in this unique case.

The case is important in that extremely long bones were detected as early as 24 weeks of gestation, along with dysmorphological features involving fetal hands and feet. The early diagnosis allowed the obstetrical team to educate the patient on potential outcomes, and prepare for delivery in an intensive care setting with a cardiology team. The evidence in this case was not sufficient to offer pregnancy termination, but this option may be considered in the future with the advent of improved diagnostic techniques and more documented neonatal outcomes.

Table 1: *Previous Sonographic Diagnosis of Congenital Marfan Disease*

Date of case	GA of initial ultrasound findings	Description of ultrasound findings	Physical findings at birth	Outcome	Genetics
2007 (7)	22	Bilateral choroid plexus cysts, mild tricuspid regurgitation, and femur length above 95%	Typical marfanoid habitus with cutis laxa, arachnodactyly and flexion contractures.	Death at 9th post-natal day due to worsening congestive heart failure.	*
1995 (8)	34	Echo: typical cardiac manifestations	*	Died at 2 months of age due to congestive heart failure.	*
2006 (9)	33 weeks	Cardiomegaly, dilated ascending aorta and pulmonary artery, pulmonary atresia, dysplastic mitral and tricuspid valves,	Post-mortem: arachnodactyly, arthrogryposis, senile looking face, hypoplastic lungs, massive heart (50g, > double the 95 percentile)	Fetus died suddenly at 39 weeks gestation	Mutation in the exon 26 of *FBN1*
1994 (10)	37	Cardiomegaly, atrioventricular valve insufficiency and dilatation of the outflow tract	*	*	*
1999, (11)	29	Cardiomegaly dilated right atrium/right ventricle, dysplastic tricuspid valve, and severe tricuspid regurgitation.	Slender fingers and toes, body length at 90%, weight <10%, aged appearance, non-paralytic hypotonia	Died at age of 3 months due to heart failure, cardiomegaly, and lobar emphysema.	Substitution of G by A at codon 1032 in exon 25 in long arm of chromosome 15. De novo mutation suggestion by absence of affected family members.
1981 (12)	24 weeks	Significantly lengthened limbs in a mother with a previously affected child.	*	*	*

*No information available.

In summary, congenital Marfan syndrome cannot be diagnosed at this time with invasive genetic testing. Careful sonographic assessment and heightened index of suspicion for abnormal limb measurements are critical in diagnosing this in utero. 3D ultrasound allows for clear visualization of the long bone and cardiac features to aid in patient education and clinical management.

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