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RESEARCH ARTICLE

Genetic Ethiology, Associated Anomalies in Fetal Aberrant Right Subclavian Artery: A Retrospective Cohort Study in a Tertiary Hospital

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Abstract

Introduction: This study aimed to determine the prevalence of chromosomal anomalies in fetuses with isolated and non-isolated aberrant right subclavian artery (ARSA) and to evaluate its association with other congenital anomalies. **Methods:** From 1 June 2021 to 1 June 2023, 47 ARSA cases were diagnosed by prenatal ultrasound in our hospital. The fetuses were divided into isolated ARSA group and non-isolated ARSA group. Among the 47 fetuses, 15 were characterized in the isolated group and 32 with combined other ultrasonic abnormalities in the non-isolated group. General information, ultrasound presentation, chromosomal findings, and birth and pregnancy outcomes were reviewed retrospectively. **Results:** In the non-isolated ARSA group, 17 cases (53,1%, 17/32) were associated with congenital heart defects, and 8 cases (25 %, 8/32) were associated with extracardiac abnormalities. Chromosome karyotype analysis was performed successfully with all 23 samples, and a total of 8 abnormalities (17 %, 8/47) were detected, including 7 cases of trisomy 21, and 1 case of trisomy 18. Single-nucleotide polymorphism array was performed in these 5 cases. Microdeletion was detected in four cases, but one of the arrays was reported normal. Using SNP-array and karyotype analysis in fetuses with ARSA, the total chromosomal anomaly detection rate was found 25.5 % (12/47). **Conclusion:** The most common malformation accompanying ARSA is cardiac abnormality. Isolated ARSA has a low risk of chromosomal abnormalities, so invasive chromosomal testing is not recommended. Non-isolated ARSA has a high incidence of chromosomal abnormalities, so early karyotyping should be recommended.

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Introduction

Aberrant right subclavian artery (ARSA) is a congenital anomaly of the aortic arch that can be seen in approximately 2 % of healthy individuals.[1,2] ARSA may be part of a complex heart malformation or genetic syndrome or a normal vascular variation. Normally, the right subclavian artery arises from the brachiocephalic trunk. In contrast, ARSA originates superior part of the descending aorta and distal to the left subclavian artery. ARSA becomes the last branch of the aortic arch and passes behind the esophagus and trachea to the right arm. The aberrant artery forms a U-shaped loop with the descending aorta. Due to this structural anatomical difference, ARSA may press on the neighboring structures of the trachea and esophagus in newborns or infancy, and may cause many symptoms including dysphagia, respiratory distress, and stridor.[3,4]

Owing to the advances in prenatal ultrasound diagnosis techniques employed, an increasing number of fetal structural malformations are being diagnosed. These advances can help clinicians create effective diagnosis and treatment plans, reduce adverse pregnancy outcomes, and prevent birth defects.[5] Fetuses with ARSA are at high risk for trisomies and copy number variation (CNV) and prenatal ultrasound can accurately diagnose fetal ARSA.[6, 7, 8] In this study, we aimed to analyze and provide information on the relationship between genetic etiology, postnatal outcomes, and prognosis of ARSA associated with isolated and/or complex anomalies.

Material and Methods

Clinical data for patients who presented to the Turkish Ministry of Health Ankara Bilkent City Hospital at the Perinatology Clinic with ARSA during ultrasound examination between 1 June 2021 and 1 June 2023 were evaluated retrospectively. The present study protocol was approved by the institutional ethics committee in suitability with the principles of the Declaration of Helsinki and approved by Ankara City Hospital Clinical Ethics Committee (Date: 21-06-2023, Number: E2-23-4352). Pregnant women with multiple pregnancies, and perinatal outcomes unknown were excluded from the study. After the participants signed the informed consent form, chorion villus sampling, amniotic fluid, or cord blood was collected for karyotype analysis and/or single nucleotide polymorphism (SNP) array based on different gestational weeks. Prenatal other cardiac and/or other ultrasound abnormalities in fetuses were collected. The cases were divided into the isolated ARSA group (n=15 cases) and the non-isolated ARSA (ARSA combined with other ultrasonic abnormalities) group (n=32 cases). All ultrasonographic measurements were performed by at least two perinatologists while the patient was looking. Fetal ultrasonography examination of all participants was evaluated using Voluson E10 (GE Medical Systems) ultrasonography device and a 3.5 MHz convex transducer (GE C2-9-D) transabdominal probe was used for the measurements. Evaluations were carried out in accordance with practice guidelines.[9],[10] ARSA leaves the descending aorta, the junction of the aortic arch and the ductal arch, passes between the trachea and the vertebrae, and extends towards the right shoulder. Ultrasonic view of fetal ARSA is shown in Figure 1. Pregnancy outcome and postnatal development of all cases with ARSA were followed from hospital records and/or by telephone.

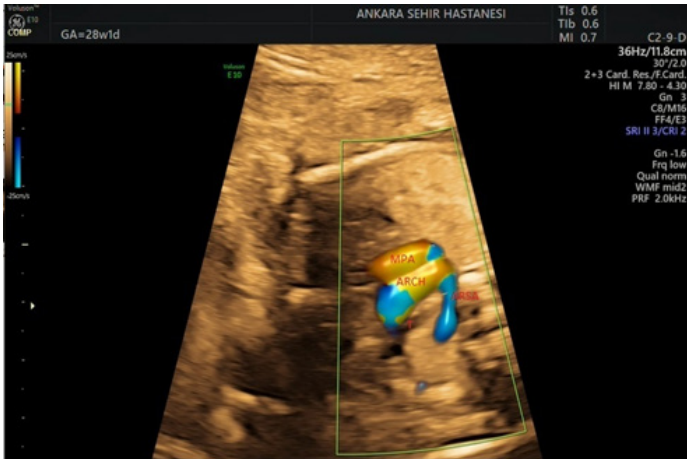

Figure 1. Ultrasound View of Fetal ARSA
Abbreviations: ARSA, aberrant right subclavian artery; MPA, main pulmonary artery; ARCH, aortic arch; T, trachea.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS v. 25, IBM, SPSS for Windows, NY: IBM Corp.). Categorical variables are presented in numbered and percentages.

Results

The fetuses were divided into isolated ARSA group and non-isolated ARSA group. Among the 47 fetuses, 15 were characterized in the isolated group and 32 with combined other ult-

Table 1. Fetuses with non-isolated ARSA (n=32)

Classification	Number of fetuses
Intrauterine Growth Restriction	1
Polyhydramnios	1
Urogenital System	
Hypospadias	1
Crossed fused renal ectopia	1
Combined with Congenital Heart Defects	
Ventricular septal defect	7
Left aortic arch	1
Right aortic arch	1
AVSD	1
TGA	1
DORV	1
Thymus hypoplasia	3
HLHS	3
Mitral dysplasia	2
Interrupted aorta	1
Anevrisma of foramen ovale	1
Ultrasonographic soft markers	
Renal pyelectasis	3
Choroid Plexus Cyst	4
Single umbilical artery	3
Echogenic Cardiac Focus	3
Clinodactyly	1
Central Nervous System	
Corpus callosum agenesia	1
Cavum vergae	1
Ventriculomegaly	2
Congenital Diaphragmatic Hernia	3
CPAM	1
Cleft lip	1
Omphalocele	1
Umbilical cord cyst	2
Eosophageal atresia	1
Pleural effusion	2
Gastrointestinal duplication cyst	1

Abbreviations: ARSA, aberrant right subclavian artery; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; CPAM, congenital pulmonary airway malformation.

rasonic abnormalities in the non-isolated group.

In the non-isolated group, 17 cases (53,1%, 17/32) were associated with congenital heart defects, and ARSA.[8] cases (25 %, 8/32) were associated with extracardiac abnormalities. Fetuses with extracardiac anomalies were associated with diaphragmatic hernia in 3 cases, congenital pulmonary airway malformation (CPAM) in 1 case, eosophageal atresia in 1 case, corpus callosum agenesia in 1 case, hypospadias and crossed fused renal ectopia in 1 case, and gastrointestinal duplication cyst in 1 case. It was together with other ultrasonographic soft markers in 7 cases (21.8 %, 7/32). The most common anomaly in fetuses with congenital heart defects is ventricular septal defect (14.8 %, 7/47) (Table 1).

In the non-isolated group, 6 patients terminated the pregnancy. Pregnant women numbered 1 and 11 shown in Table 2, gestational week at birth was 31 and 34 weeks of gestation, respectively. Other pregnant women's gestational week at birth were at the term, and the primary cesarean section rate was 25% (8/32). On the other hand, the gestational week at birth of all pregnant women in the isolated group was at term, and the primary cesarean section rate was 26% (4/15).

Chromosome karyotype analysis was performed successfully with all 23 samples, and a total of 8 abnormalities (17 %, 8/47) were detected, including 7 cases of trisomy 21, and 1 case of trisomy 18 (Table 2).

Normal chromosomal karyotype analysis was reported in 12 cases in the non-isolated group. SNP array was performed for 5 of these fetuses. 22q11.2 deletion was reported for 3 cases (3/5), 11q24.2q25

Table 2. Karyotype analysis detected in fetus with ARSA

Case	Karyotype analysis(CNV)	SNP-Array	Ultrasonic phenotype	Perinatal outcomes
1	47, X*, +21		ARSA, pleural effusion, ventricular septal defect	Postnatal exitus
2	47, X*, +21		ARSA, complet atrioventricular septal defect	Postnatal exitus
3	47, X*, +21		ARSA, bilateral clinodactyly, cavum vergae, perimembranous ventricular septal defect	TOP
4	47, X*, +21		ARSA, absent nasal bone, hyperechogenic cardiac focus, ventricular septal defect	TOP
5	47, X*, +21		ARSA, absent nasal bone, hyperechogenic bowel, single umbilical artery	TOP
6	47, X*, +21		ARSA, complete atrioventricular septal defect, umbilical cord cyst, umbilical hernia, single umbilical artery, bilateral clenched hand, thymus hypoplasia, syndactyly, absent gallbladder	Postnatal exitus
7	47, X*		ARSA, eosophageal atresia, polyhydramnios, pouch sign	Postnatal exitus
8	47, X*, +18		ARSA, omphalocele, clenched hand, rocker-bottom foot, choroid plexus cyst	TOP
9	46, X*	22q11.2 deletion	ARSA, double outlet right ventricle	
10	46, X*	22q11.2 deletion	ARSA, interrupted aortic arch, perimembranous ventricular septal defect	TOP
11	46, X*	22q11.2 deletion	ARSA, thymus hypoplasia, mitral valve dysplasia, interrupted aortic arch, severe tricuspid valve regurgitation	Postnatal exitus
12	46, X*	11q24.2q25 deletion	ARSA, pleural effusion, ventricular septal defect	
13	46, X*		ARSA, diaphragmatic hernia, bilateral cleft lip and palate, inlet ventricular septal defect	TOP
14	46,X*		ARSA, Transposition of the great arteries, thymus hypoplasia	
15	46, X*	Normal	ARSA, hypoplastic left heart, aortic arch hypoplasia, persistent left superior vena cava, cystic hygroma	Postnatal exitus
16	46, X*		ARSA, congenital pulmonary airway malformation	
17	46,X*		ARSA, ileal atresia, gastrointestinal duplication cyst	
18	46, X*		ARSA, crossed-fussed renal ectopia, choroid plexus cyst	
19	46, X*		ARSA, ventricular septal defect, hyperechogenic cardiac focus, hyperechogenic bowel	
20	46, X*		ARSA, polyhydramnios, hypospadias	
21	46, X*		ARSA(isolated)	
22	46, X*		ARSA(isolated)	
23	46, X*		ARSA(isolated)	

Abbreviations: CNV, copy number variant; ARSA, aberrant right subclavian artery; TOP, termination of pregnancy; SNP, single nucleotide polymorphism; NCK, Normal Constitutional Karyotype.

deletion was reported for 1 (1/5) case and normal array was reported normal for 1 (1/5) case (Table 2).

In the isolated ARSA group, 3 pregnant women performed prenatal invasive testing and no chromosomal abnormality was detected (Table 2).

In the non-isolated case group, 12 pregnant women did not have prenatal diagnosis tests. No chromosomal anomaly was found in any of these 12 cases in postnatal evaluation.

Using SNP array and karyotype analysis in fetuses with ARSA, the total chromosomal anomaly detection rate was found 25.5% (12/47) as observed (Table 3).

Table 3. Phenotypic characteristics of 47 fetuses with ARSA

	Number of fetuses	Number of pathogenic CNV and/or SNP array
Fetuses with isolated ARSA	15	0(0 %)
Fetuses with non-isolated ARSA	32	12(37,5 %)
Total	47	12(25,5 %)

Abbreviations: ARSA, aberrant right subclavian artery; CNV, copy number variant; SNP, single nucleotide polymorphism.

Discussion

With the development of ultrasound technology and the improvement in the understanding of fetal ARSA, the rate of prenatal detection is increasing day by day. In some studies, ARSA has been closely associated with chromosomal abnormalities, and trisomy 21 has been reported in these cases.[11,12] In this study, chromosomal abnormalities were detected in eight cases by karyotype analysis. However, in four cases with ARSA with additional abnormal ultrasound findings and no chromosomal abnormality detected, SNP array was used and detected microdeletion. Conventional karyotype analysis can detect chromosomal fragment abnormalities above a certain size, whereas SNP-array sequence can detect smaller and lower copy number abnormalities as well as normal copy number abnormalities.[13,14] Therefore, SNP array may provide additional benefits and be more advantageous in the etiological detection of fetuses with isolated or non-isolated ARSA.

Some researchers have reported cases of trisomy 21 in fetuses with isolated ARSA. Therefore, they suggest that ultrasound can be used as a soft marker for prenatal screening of ARSA fetal chromosomal abnormalities and prenatal chromosomal examination, even if isolated.[15,16,17] Conversely, other studies do not recommend invasive prenatal testing for fetuses with isolated ARSA unless accompanied by additional ultrasound abnormalities.[18] It has been reported in previous studies that the presence of ARSA increases the risk of trisomy 21 syndrome.[19,20] In this study, trisomy 21 syndrome was detected in seven fetuses with ARSA with additional abnormal ultrasound findings, consistent with previous studies. Four of the fetuses diagnosed with trisomy 21 died due to additional severe anomalies in the postpartum period. Three pregnant women, who were found to have ARSA and whose chromosome analysis was reported as trisomy 21, decided to terminate the pregnancy. In this study, trisomy 18 syndrome was detected in one fetus with ARSA and additional ultrasound finding such as omphalocele, clenched hand, rocker-bottom foot, choroid plexus cyst, and pregnacy was terminated in this case.

ARSA is also associated with 22q11 deletion syndrome .[21] The Di-George syndrome is a multisystemic condition that features cardiac malformations, velopharyngeal insufficiency, hypoparathyroidism with hypocalcemia, and thymic aplasia with immune deficiency .[22,23] Three fetuses with ARSA were also diagnosed with 22q11.2 in this study. There were additional fetal cardiac anomalies in these cases. One pregnant decided to terminate, and one of the fetuses died after delivery. The other case with a diagnosis of 22q11.2 and a double outlet right ventricle additional cardiac anomaly continues to be followed up by pediatrics and was operated by cardiovascular surgery after delivery.

11q deletion, also known as Jacobsen syndrome, is a disorder of developmental delay, growth retardation, thrombocytopenia, dysmorphic features, cardiac abnormalities, and other congenital anomalies.[24] In our study, 11q24.2q25 deletion was detected with SNP array in one case with ARSA, pleural effusion, and ventricular septal defect. Prognosis and genetic counseling were given to the patient in the prenatal period and the patient decided to continue the pregnancy. The follow-up continues in the postnatal period.

Non-invasive prenatal screening tests with a high accuracy rate for chromosomal abnormalities can be offered as an alternative for patients with abnormal ultrasound findings and who do not want to perform an invasive test.[25] Non-invasive prenatal screening test was performed in 5 of 12 cases in the non-isolated group, and all of the results were reported as low risk.

One study reported that ARSA may be the only ultrasound finding in trisomy 21 as well as Di-George and Turner syndrome. Therefore, it was emphasized that ARSA screening should be a part of fetal anatomical evaluation, and standard karyotyping and FISH analysis should be recommended in patients even with isolated ARSA.[26] In our study, in isolated group, four patients who did not want to perform invasive test had non-invasive prenatal screening test and the results were reported as low risk. Similarly, no abnormal chromosomal anomaly was found in the postnatal evaluations of isolated patients.

Our study also has some limitations. The relatively low number of cases can be considered as the main limitation. Mutations in a single gene can also be the cause underlying ARSA. Therefore, in the future, the methodology can be improved by adding whole-exome sequencing analysis with multicenter high-case groups.

Conclusion

ARSA is a common soft ultrasound marker. Fetuses with isolated ARSA have a low probability of being detected with pathogenic chromosomal karyotype. Conversely, when ARSA is non-isolated and observed with other ultrasound abnormalities, the risk of pathogenic chromosomal karyotype analysis is increased remarkably. It should be informed that the possibility of chromosomal anomaly is low in isolated ARSA cases, there may be an abnormal analysis result, it is an ultrasonic soft marker, and an invasive test can be performed if desired. In these cases, prenatal genetic counseling and SNP array should be recommended to better assess fetal prognosis.

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