VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2020, vol. 91, no. 8, 460–464

ISSN 0017–0011

DOI: 10.5603/GP.2020.0078

The association between aberrant right subclavian artery and trisomy 21 in a tertiary center in Turkey

Mete Sucu, Mehmet Ozsurmelil, Erol Arslan, Cansun Demir, Cüneyt Evrüke

Cukurova University; Faculty of Medicine; Department of Obstetrics and Gynecology, Adana, Turkey

ABSTRACT

Objectives: We hoped to reveal the frequency of Aberrant Right Subclavian Artery (ARSA) and to find the relationship of isolated/non-isolated ARSA with chromosomal defects and other fetal congenital heart diseases (FCHD) in a heterogeneous population.

Material and methods: This was a retrospective cohort study conducted between December 2015 to September 2018. Women admitted for routine ultrasound examination or referred to our hospital for a suspected fetal anomaly were underwent detailed fetal anomaly ultrasonography scan and tested for the presence of ARSA.

Results: ARSA was detected in 27 patients and an isolated finding in 13 (48%) cases. Among 13 cases with isolated ARSA, trisomy 21 was diagnosed in 1 case. In the non-isolated group (n: 14, 52%), five cases presented with trisomy 21. There was no significant difference of trisomy 21 frequency between isolated and non-isolated groups (7.6% vs 35.7%, p = 0.08). In 3 patients, FCHD was diagnosed and 2 of them had trisomy 21.

Conclusions: Our study shows that ARSA can be the only marker in trisomy 21. The examination of the subclavian artery must be a part of the fetal anomaly ultrasonography. Detecting an ARSA should increase the attentiveness of the sonographer to investigate for the other markers of trisomy 21. In the existence of other findings, invasive diagnostic procedures should be offered to the patients, whereas in cases that arsa is the only finding, other risk factors should be investigated to offer karyotyping or cell-free DNA analysis.

Key words: ARSA; trisomy 21; isolated; karyotyping; ultrasound

Ginekologia Polska 2020; 91, 8: 460–464

INTRODUCTION

Aberrant right subclavian artery(ARSA) is the common seen abnormality or a variant of the aortic arch occurring in 0.5% to 1.4% of the normal adult population [1]. ARSA is featured by different origination of the right subclavian artery from descending aorta directly instead of the brachiocephalic trunk. Normally, the left aortic arch gives three branches, whereas with ARSA four vessels arise from the aortic arch; the right common carotid artery, the left common carotid artery, the left subclavian artery, and the ARSA, respectively [2, 3]. ARSA comes up from the distal portion of the aortic arch, and its route continues backwards the esophagus and the trachea and goes to the right shoulder (Fig. 1A and 1B).

Most of the adult patients with ARSA have no symptoms, and it is usually a benign pathology. However, in some cases, it can cause dysphagia and partial airway obstruction due to the compression esophagus and trachea [4].

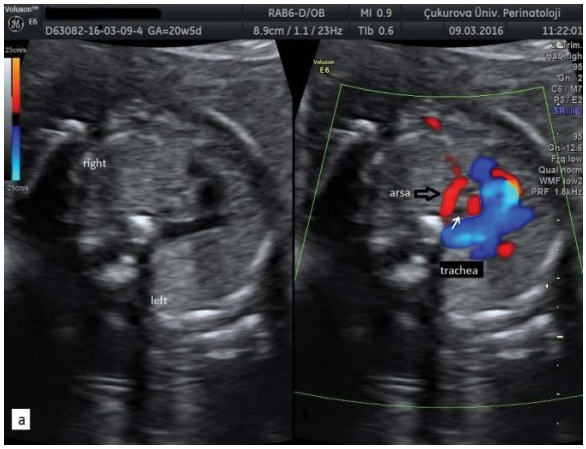

Figure 1A. Three-vessel trachea view showing aberrant right subclavian artery arising from the aorta and continuing behind the trachea

Corresponding author:
Mete Sucu
Cukurova University; Faculty of Medicine; Department of Obstetrics and Gynecology, 01330 Saricam, Adana, Turkey
phone: +90 322 3386060-3195-3196, fax: 90 322 3386527, mobile: +905056176538
e-mail: metesucu@yahoo.com

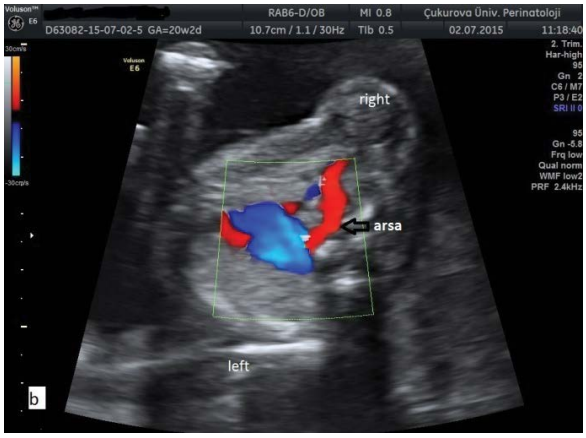

Figure 1B. The vessel heads towards the right upper arm

It was reported that ARSA may be a marker for trisomy 21 such as absent nasal bone or thickened nuchal translucency [5–7]. Furthermore, the association between ARSA and 22q11 microdeletion syndrome has also been reported [8]. However, it is important to keep in mind that ARSA can also be an isolated finding without any association with cardiac or extra-cardiac malformations.

In our study we aimed to determine the frequency of isolated/non-isolated ARSA among a heterogenic population and to study its relation with chromosomal abnormalities, as well as different congenital anomalies including fetal congenital heart diseases (FCHD).

MATERIAL AND METHODS

This was a retrospective cohort study conducted in Cukurova University Faculty of Medicine between December 2015 and September 2018. The study included women attended our Fetal Medicine Clinic for routine second-trimester fetal anomaly scanning or sent to our hospital during the second/third trimester of pregnancy for a possible fetal anomaly or positive aneuploidy screening. All patients underwent a detailed fetal anomaly scan and were checked for the presence of ARSA. The findings of anomaly scan; presence of soft markers, cardiac and extracardiac congenital malformations, were noted. This was a heterogenous population including both low and high-risk patients. All patients were evaluated by four experienced observers using VolusonE6(GE Medical Systems, Zipf, Austria) with a transabdominal 4–8-MHz probe. The study was approved by the local ethics committee of Cukurova University Faculty of Medicine(approval number: 02.02.2018 74-2). All patients gave written informed consent for their data to be used.

Soft USG markers were as increased nuchal fold, hyperechogenic bowel, echogenic intracardiac focus, hypoplastic/absent nasal bone, renal pyelectasis, shortened long bones(femur-humerus) and choroid plexus cyst.

Ultrasound technique for the diagnosis of ARSA

The three-vessel-trachea view is optimal for the diagnosis of ARSA. ARSA is demonstrated from the intersection of the aortic arch and ductus arteriosus with a course backward the trachea toward the right shoulder and arm. To demonstrate its anomalous origin on the aortic arch and its retrotracheal course toward the right shoulder, colour-Doppler must be applicated in the three vessels and trachea view [2]. Pulsed-wave Doppler can be used to discriminate ARSA with the azygos vein, which courses to the right of the trachea. When ARSA was detected, it was also confirmed in the longitudinal aortic arc view [3]. These complementary approaches help to confirm the diagnosis of ARSA.

Fetal karyotyping with amniocentesis (cytogenetic analyses and 22q11 microdeletion) was discussed with the parents when ARSA was diagnosed. All maternal-perinatal data were noted during ultrasound examination and after birth. In all cases where the karyotype was not performed prenatally, if the newborn had doubtful characteristics of a chromosomal anomaly, a peripheral blood karyotype test was performed. The karyotype was noted normal if the newborn had normal findings of physical examination. All the patients having a major fetal cardiac abnormality underwent both fetal and postnatal echocardiography by a pediatric cardiologist experienced with diagnosing fetal congenital heart anomalies. The diagnosis of isolated ARSA was done in accordance with the nonexistence of other ultrasound signs suggesting chromosomal abnormalities and/or fetal structural malformations after complete prenatal and postnatal evaluation. All cases of ARSA were confirmed by postnatal echocardiography.

All information of patients(including gestational age at diagnosis, delivery week, karyotype, 22q11 microdeletion, extra-cardiac malformations, additional cardiac findings, and postnatal outcome) were recorded and analyzed.

Descriptive statistics were done using Microsoft Excel. The Chi-square test was used for the comparison. A p-value < 0.05 was considered to indicate statistical significance.

RESULTS

A total of 5283 fetuses were examined during the second or third trimester of pregnancies for a suspected fetal anomaly or routine ultrasound examination. The median gestational age was 23 weeks at diagnosis. The median age of the patients with ARSA was 30 years. ARSA was detected in 27 cases (0.51%). ARSA was an isolated finding in 13 (48%) cases whereas in 14 cases (52%) ARSA was a non-isolated finding. In three cases (11.1%), ARSA was accompanied by other cardiac defects, whereas in six cases (22.2%) soft sonographic markers were observed. Extracardiac malformations were present in four fetuses (14.8%). In one case (3.7%), only fetal growth restriction (FGR) accompanied ARSA. Clinical, demographic and USG findings are shownin Table 1.

Table 1. Cases with aberrant right subclavian artery

	Maternal age [years]	Gestational age at diagnosis [weeks]	Delivery time [weeks]	Additionalcardiac findings	Extracardiac findings	Karyotype	22q11.2 microdeletion	Postnatal outcome
1	25	20	42	none	none	normal	negative	Healthy, 15 months old
2	39	22	39	none	none	normal	negative	Healthy, 16 months old
3	26	20	39	none	none	NP	NP	Normal karyotype has dysphagia, 18 months old
4	29	23	39	none	none	NP	NP	Healthy, normal karyotype, 13 months old
5	24	21	37	none	none	Tri21	negative	Tri21, 7 months old
6	34	25	32	none	none	NP	NP	Healthy, normal karyotype, 12 months old
7	32	20	37	none	none	normal	negative	Healthy, 13 months old
8	32	24	38	none	none	normal	negative	Healthy, 11 months old
9	38	20	37	none	none	normal	negative	Healthy, 15 months old
10	27	25	25	AVSD, PLSVC, DORV, PS	SUA	Tri21	negative	Intrauterine exitus
11	21	23	41	none	mild VM	NP	NP	Healthy, normal karyotype, 7 months old
12	27	22	40	none	none	NP	NP	Healthy 6 months old
13	43	20	36	AVSD, BA	mild VM, CLP, SUA	NP	NP	Tri21, 5 months old
14	24	24	41	none	VM, CLP, HB	normal	NP	Postnatal exitus on the 1st day
15	34	25	34	none	MCM, DA, NBH	Tri21	NP	Intrauterine exitus
16	34	21	33	none	CPC, NBH	Tri21	NP	Tri21,16 months old
17	28	27	37	none	FGR, HB	NP	NP	Healthy, normal karyotype, 9 months old
18	39	23	33	none	NBH, DB, SG, SF	Tri21	NP	Tri 21, 9 months old
19	26	23	40	none	HB, NBH	normal	NP	Unknown
20	35	23	39	none	RP, INF,NBH	normal	NP	6 months old, operated for UPJO
21	21	26	41	none	RP	NP	NP	Healthy, normal karyotype, 30 months old
22	30	22	40	none	none	NP	NP	Healthy, normal karyotype, 28 months old
23	37	19	38	none	INF	normal	NP	Unknown
24	20	24	39	none	none	normal	NP	Healthy, 32 months old
25	31	25	40	none	none	NP	NP	Healthy, normal karyotype, 24 months old
26	33	27	39	none	SUA	normal	NP	Healthy, 36 months old
27	28	21	33	VSD	none	normal	negative	Healthy, 33 months old

NP — not performed; AVSD — atrioventricular septal defect; PLSVC — persistent left superior vena cava; DORV — double outlet right ventricle; PS — pulmonary stenosis; SUA — single umbilical artery; VM — ventriculomegaly; BA — bradiarithymi; CLP — cleft lip palate; MCM — mega cysterna magna; DA — duodenal atresia; NBH — nasal bone hypoplasia; CPC — choroid plexus cyst; FGR — fetal growth restriction; INF — increased nuchal fold; DB — dilatated bowel; SF — short femur; SG — sandal gap; HB — hyperechogenic bowel; RP — renal pelviectasia, VSD — ventricular septal defect; UPJO — ureteropelvic junction obstruction

Prenatal karyotype analyses were performed in seven patients with isolated ARSA (53.8%) and revealed trisomy 21 in 1 case. Postnatal evaluation of other patients with isolated ARSA was normal for trisomy 21.

In the non-isolated group, eight patients (57.1%) accepted prenatal karyotyping, and trisomy21 was diagnosed in four cases. In the postnatal evaluation of other six fetuses of the non-isolated group, the karyotype analysis result of five fetuses were noted normal because of the nonexistence of postnatal clinical findings suggesting choromosomal anomaly whereas 1 patient had clinical features of trisomy 21 and karyotype analysis revealed trisomy 21.

The frequency of trisomy 21 was 7.6% (1/13) in the isolated group, and 35.7% (5/14) in the non-isolated group, and the difference was not statistically significant (p = 0.08). In total, six cases with the diagnosis of ARSA were found to have trisomy 21 (22%).

In the total study group, 31 fetuses had trisomy21 with the rate of 0.58% (31/5283). Among 31 fetuses with trisomy 21, 6 fetuses had ARSA with the rate of 19.3% (6/31). In one of them ARSA was an isolated finding. ARSA rate was 0.39% (21/5252) in patients without trisomy 21. Trisomy 21 rate of patients with ARSA was 0.222 (6/27) whereas patients without ARSA had a trisomy 21 rate as 0.004% (25/5256) and there was a 47 fold increase of trisomy 21 in patients with ARSA.

DISCUSSION

The prevalence of ARSA was 0.51% in our study population, which consists of both low and high-risk patients in a tertiary unit in Turkey. ARSA was an isolated finding in 13 of 27 (48%) fetuses. Six fetuses had soft sonographic markers, three fetuses had other cardiac malformations, and four fetuses had extra-cardiac malformations.

There is an ongoing debate about whether invasive diagnostic procedures are indicated when ARSA is noted as an isolated finding. The relationship between ARSA and trisomy 21 was first described by Chaoui et al. [2]. These authors identified ARSA in 35.7% of fetuses with trisomy 21 during the second and third trimester (5 of 14). We identified ARSA in 19.3% of fetuses with trisomy 21. Since then, ARSA was reported as one of the most powerful independent markers of trisomy 21 [7, 9, 10]. Agathokleous et al. [9] reported that trisomy 21 risk was increased about 3- to 4-fold in patients with ARSA but they emphasized that most of the studies in their meta-analysis were done in high-risk pregnancy groups. In our population trisomy 21 rate was 47 fold increased in patients with ARSA.

De Leon-Luis et al. [11] studied a large unselected population and found 60 ARSA cases among 8781 fetuses, with a prevalence of 0.7%, which was higher than our study. Trisomy21 was diagnosed in seven(12%) of the 60 cases, all were in the non-isolated group(21 fetuses) and associated with the strong markers of trisomy21, such as absent or hypoplastic nasal bone, nuchal fold thickness, cystic hygroma, and ventriculomegaly, which also indicate performing karyotype analysis. Trisomy21 rate of their patients with non-isolated ARSA was 33.3% and similar to our study with rate of 35.4%. Whereas in our study isolated ARSA group had a 7.6% trisomy21 rate, in their study no cases of trisomy21 were detected in fetuses with isolated ARSA. We evaluated the role of ARSA without USG markers associated with Trisomy21 and our data suggests that additional markers should be searched in these patients and family should be informed about trisomy21 risk. Even in the patients with isoleted ARSA increased trisomy21 risk must be taken into account.

Paladini et al. [7] studied a large trisomy21 group and found the incidence of 25% for ARSA. Borenstein et al. [12] and Paladini et al. [7] found that ARSA increased the risk of trisomy21 by about 16- to 20-fold.

Paladini et al. [7] diagnosed ARSA in 27 fetuses among the 106 fetuses with trisomy21; ARSA was the only finding in eight (30%) of these fetuses. Similarly we diagnosed ARSA in 6 fetuses among the 31 fetuses with trisomy21 and ARSA was the only finding in one of these cases. Based on these findings, they recommended that prenatal karyotyping analysis could be performed even in the cases of isolated ARSA [7]. Similarly, in the study of Gul et al. [13], the authors found Trisomy21 in one case of nine cases with isolated ARSA. In our study, one case (7.6%) presented with Down syndrome among the 13 cases with isolated ARSA.

While recommending amniocentesis for isolated ARSA cases, other risk factors should also be considered. Similarly, Esmer et al. [14] diagnosed trisomy21 with isolated ARSA in six fetuses; however, four cases had a positive first/second trimester screening test for trisomy21, and the remaining two of them had advanced maternal age. In three previous series, no case of trisomy21 with isolated ARSA was existed[6,15,16]. Yazicioglu et al. [6] concluded that the presence of ARSA without other sonographic findings is not a strong marker to recommend karyotyping and cell-free fetal DNA can be an alternative approach for these patients. In our study 7.6% of patients with isolated ARSA had trisomy21. According to these findings we suggest to explore additional risk factors to offer karyotyping or cell-free fetal DNA.

Our findings show that nasal bone hypoplasia and single umbilical artery were the most frequent additional findings to ARSA, with rates of 18.5% and 11.1%, respectively. Therefore, we agree with the idea of recommending karyotype analyses to the ARSA cases with additional findings. On the other hand, for the cases of isolated ARSA, screening test results should also be taken into account.

The close relationship between conotruncal anomalies and 22q11.2 microdeletion has been shown, especially if aortic arch anomalies (*i.e.,* interrupted aortic arch, tetralogy of Fallot,ARSA, etc.) are existing additionally [8]. In our study, we also investigated the existence of 22q11.2 microdeletion besides the conventional cytogenetic analyses. Eight patients accepted microdeletion analyses, but no cases were detected to have 22q11.2 microdeletion. In the study of Rembouskos et al. [8], 22q11.2 microdeletion was catched in a case of ARSA with increased nuchal translucency. The authors suggested that FISH analyses for this microdeletion can be added to the cytogenetic analyses, even if there are no other cardiac defects that accompany ARSA. We believe that more prospective studies are needed to predicate the

relation between 22q11.2 microdeletion and ARSA without cardiac defects before it becomes an additional routine test.

One of the limitations of our study was the retrospective design of the study and low number of patients used to determine the prevalence of associated structural and chromosomal anomalies, microdeletion 22q11.2. In future work, more patients with isolated ARSA would be needed to determine the value of routine cytogenetic analyses for these patients.

CONCLUSIONS

In conclusion, the visualization of the right subclavian artery is likely a valuable marker especially in patients with additional USG findings for trisomy 21 and should be a part of extended basic cardiac screening. The detection of ARSA should alert the examiner to seek additional sonographic markers. In existence of other signs suggesting trisomy21, we must offer invasive diagnostic procedures to the patients. Whereas in isolated cases, risk factors should be incorporated into the discussion about karyotype analyses or cell-free fetal DNA should be considered as a choice.

Conflict of interest

All authors declared that they have no conflict of interest.

REFERENCES

1. Zapata H, Edwards JE, Titus JL. Aberrant right subclavian artery with left aortic arch: associated cardiac anomalies. Pediatr Cardiol. 1993; 14(3): 159–161, doi: 10.1007/BF00795645, indexed in Pubmed: 8415218.
2. Chaoui R, Heling KS, Sarioglu N, et al. Aberrant right subclavian artery as a new cardiac sign in second- and third-trimester fetuses with Down syndrome. Am J Obstet Gynecol. 2005; 192(1): 257–263, doi: 10.1016/j.ajog.2004.06.080, indexed in Pubmed: 15672034.
3. Chaoui R, Rake A, Heling KS. Aortic arch with four vessels: aberrant right subclavian artery. Ultrasound Obstet Gynecol. 2008; 31(1): 115–117, doi: 10.1002/uog.5240, indexed in Pubmed: 18098341.
4. Carrizo GJ, Marjani MA. Dysphagia lusoria caused by an aberrant right subclavian artery. Tex Heart Inst J. 2004; 31(2): 168–171, indexed in Pubmed: 15212130.
5. Hara M, Satake M, Itoh M, et al. Radiographic findings of aberrant right subclavian artery initially depicted on CT. Radiat Med. 2003; 21(4): 161–165, indexed in Pubmed: 14514122.
6. Fe, Sevket O, Akin H, et al. Aberrant right subclavian artery in Down syndrome fetuses. Prenat Diagn. 2013; 33(3): 209–13.
7. Paladini D, Sglavo G, Pastore G, et al. Aberrant right subclavian artery: incidence and correlation with other markers of Down syndrome in second-trimester fetuses. Ultrasound Obstet Gynecol. 2012; 39(2): 191–195, doi: 10.1002/uog.10053, indexed in Pubmed: 21793087.
8. Rembouskos G, Passamonti U, De Robertis V, et al. Aberrant right subclavian artery (ARSA) in unselected population at first and second trimester ultrasonography. Prenat Diagn. 2012; 32(10): 968–975, doi: 10.1002/pd.3942, indexed in Pubmed: 22847746.
9. Agathokleous M, Chaveeva P, Poon LCY, et al. Meta-analysis of second-trimester markers for trisomy 21. Ultrasound Obstet Gynecol. 2013; 41(3): 247–261, doi: 10.1002/uog.12364, indexed in Pubmed: 23208748.
10. Scala C, Leone Roberti Maggiore U, Candiani M, et al. Aberrant right subclavian artery in fetuses with Down syndrome: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015; 46(3): 266–276, doi: 10.1002/uog.14774, indexed in Pubmed: 25586729.
11. De León-Luis J, Gámez F, Bravo C, et al. Second-trimester fetal aberrant right subclavian artery: original study, systematic review and meta-analysis of performance in detection of Down syndrome. Ultrasound Obstet Gynecol. 2014; 44(2): 147–153, doi: 10.1002/uog.13336, indexed in Pubmed: 24585513.
12. Borenstein M, Minekawa R, Zidere V, et al. Aberrant right subclavian artery at 16 to 23 + 6 weeks of gestation: a marker for chromosomal abnormality. Ultrasound Obstet Gynecol. 2010; 36(5): 548–552, doi: 10.1002/uog.7683, indexed in Pubmed: 20503237.
13. Gul A, Corbacioglu A, Bakirci IT, et al. Associated anomalies and outcome of fetal aberrant right subclavian artery. Arch Gynecol Obstet. 2012; 285(1): 27–30, doi: 10.1007/s00404-011-1907-9, indexed in Pubmed: 21487731.
14. Esmer AC, Gul A, Nehir A, et al. Detection rate of trisomy 21 in fetuses with isolated and non-isolated aberrant right subclavian artery. Fetal Diagn Ther. 2013; 34(3): 140–145, doi: 10.1159/000354650, indexed in Pubmed: 24051543.
15. Willruth AM, Dwinger N, Ritgen J, et al. Fetal aberrant right subclavian artery (ARSA) - a potential new soft marker in the genetic scan? Ultraschall Med. 2012; 33(7): E114–E118, doi: 10.1055/s-0029-1245935, indexed in Pubmed: 21614745.
16. Zalel Y, Achiron R, Yagel S, et al. Fetal aberrant right subclavian artery in normal and Down syndrome fetuses. Ultrasound Obstet Gynecol. 2008; 31(1): 25–29, doi: 10.1002/uog.5230, indexed in Pubmed: 18098348.