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Case Report

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A case of Roberts syndrome: its ultrasonographic characteristics and genetic diagnosis

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Abstract

Objective: Roberts syndrome is a very rare genetic disease, and it has an autosomal recessive inheritance pattern. It develops as a result of the mutation in ESCO2 gene located in the 8th chromosome. In our study, we aimed to present a case which was found to have Roberts syndrome coexisting with multiple anomalies, particularly skeletal system anomaly, in the 17 weeks of gestation.

Case: In the fetal ultrasonographic evaluation performed on the pregnant women who referred to our hospital for routine gestational examination in the 17 weeks of gestation, anomalies in the bilateral upper and lower extremities, contracted legs, bilateral cleft palate and lip, intrauterine growth restriction and cardiac anomaly were found in the fetus. Roberts syndrome was considered first with these ultrasonographic findings. The diagnosis of Roberts syndrome was confirmed by cytogenetic and molecular analyses. Early segregation of centromeres and early breaking up of heterochromatic regions near centromeres were found at metaphase stage. By cytogenetic and molecular analyses, homozygous mutation in ESCO2 gene of the fetus and heterozygous mutation in the parents were found. The termination of pregnancy was decided after the genetic consultation with the parents. Physical examination findings and prenatal ultrasound findings after termination were found similar.

Conclusion: Many severe skeletal dysplasia cases can be diagnosed ultrasonographically before 20 weeks of gestation. Early diagnosis ensures to take necessary actions for medical support during postnatal period and in terms of labor if pregnancy continues as well as genetic consultation opportunity. If the genetic disease that causes skeletal dysplasia can be identified and parents are found to have this gene, healthy pregnancies can be achieved by obtaining normal embryos via pre-implantation genetic diagnosis in order to prevent the relapse of the disease.

Keywords: Roberts syndrome, ESCO2 gene, skeletal malformations.

Özet: Roberts sendromu olgusu: Ultrasonografik özellikleri ve genetik tanısı

Amaç: Roberts sendromu çok nadir bir genetik hastalık olup otozomal resesif kalıtım paternine sahiptir. 8. kromozomda yerleşen ESCO2 genindeki mutasyon sonucu gelişir. Çalışmamızda, 17. gebelik haftasında iskelet sistemi başta olmak üzere multipl anomalilerin eşlik ettiği Roberts sendromu saptanan bir olguyu sunmayı amaçladık.

Olgu: On yedinci gebelik haftasında rutin gebelik muayenesi için hastanemize başvuran gebede yapılan fetal ultrasonografik değerlendirmede fetüste bilateral üst ve alt ekstremitelerde anormallik, kontrakte bacaklar, bilateral yarık damak-dudak, intrauterin büyüme kısıtlılığı ve kardiyak anomali saptandı. Bu ultrasonografik bulgularla ön planda Roberts sendromu düşünüldü. Sitogenetik ve moleküler analizlerle Roberts sendromu tanısı doğrulandı. Metafaz evresinde sentromerlerin erken ayrışması ve sentromer yanındaki heterokromatik bölgelerin erken dağılımı saptandı. Sitogenetik ve moleküler analizler ile fetüste ESCO2 geninde homozigot mutasyon ve ebeveynlerde ise heterozigot mutasyon belirlendi. Ebeveynler ile genetik konsültasyon sonrası gebeliğin terminasyonuna karar verildi. Terminasyon sonrası fizik muayene bulguları ile prenatal ultrasonografik bulgular benzer saptandı.

Sonuç: Yirminci gebelik haftası öncesinde ultrasonografik olarak birçok ciddi iskelet displazisine tanı konulabilir. Erken tanı, genetik konsültasyon olanağının yanı sıra gebeliğin devamı halinde doğum açısından ve postnatal dönemde tıbbi destek için gerekli tedbirlerin alınmasını sağlar. Eğer iskelet displazisine yol açan genetik hastalık tespit edilip ebeveynlerde bu genin taşıyıcılığı saptanırsa hastalığın tekrarlamasını engellenmek için preimplantasyon genetik tanı ile normal embriyolar elde edilerek sağlıklı gebelikler oluşturulabilir.

Anahtar sözcükler: Roberts sendromu, ESCO2 geni, iskelet malformasyonları.

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Introduction

Roberts syndrome (synonym: hypomelia-hypotrichosis-facial hemangioma syndrome, pseudothalidomide syndrome, Appelt-Gerken-Lenz syndrome) is a genetic disease with autosomal recessive inheritance pattern which can be accompanied with extremity anomalies (bilateral symmetric tetraphocomelia or hypomelia in which mesomelic shortness is seen, thumb aplasia or hypoplasia and oligodactyly, syndactyly, clinodactyly, and flexion contractures in wrist and knee), craniofacial findings (microcephaly or cleft palate and lip), and cardiac, renal and neurodevelopmental retardation which progress from mild to severe levels during prenatal and postnatal periods.[1–4] The incidence of carrying Roberts syndrome and the prevalence of the disease are not known.[5] This syndrome was first defined by John Roberts in 1919 and about 150 cases have been reported so far.[4,5] Familial genetic heritance is common, and this syndrome develops as a result of the mutation of ESCO2, which is the gene of establishment of cohesion 1 homolog, coding the protein that has a role in the cohesion of sister chromatids during mitosis.

The ultrasonographic examination of fetus at second trimester helps to identify many structural and functional anomaly. In this case report, we presented a case with intrauterine Roberts syndrome together with ultrasonographic, radiological, cytogenetic and molecular findings.

Case Report

Twenty-eight-year-old multigravida patient (gravida 3, parity 1) applied to our clinic at 17 weeks and 2 days of gestation for routine gestational examination. The patient had a second-degree consanguineous marriage, but did not have any additional known disease. Her child from her first pregnancy was 4 years old and did not have any health problem. In her second pregnancy, the pregnancy was terminated due to phocomelia in the lower and upper extremities, hypertelorism and bilateral cleft palate and lip. We could not find any genetic analysis for the terminated pregnancy. There was no exposure to teratogenic agent or any medical disease such as diabetes mellitus, hypertension and heart disease in her maternal anamnesis.

A singleton live pregnancy was found in the ultrasonographic examination (Voluson E8, GE Healthcare, Milwaukee, WI, USA) where fetal biometric measurements were below 3rd percentile. While advanced level shortness was found in both humeri, absence in the unilateral ulna, radius and fibula (**Fig. 1**), and advanced level of shortness in other ulna and radius were observed (**Fig. 2**). Bilateral cleft palate and lip (**Fig. 3**), low-set ears and contracted legs were found, and bilateral femur lengths were measured below 3rd percentile. As penis length was above 95th percentile, macropenis diagnosis was established.

A fourth vessel was found in three-vessel trachea view in the fetal echocardiographic examination. As the direction of blood flow was same with superior vena cava and no innominate vein was observed in Doppler ultrasonography, it was seen that this vessel was persistent left superior vena cava.

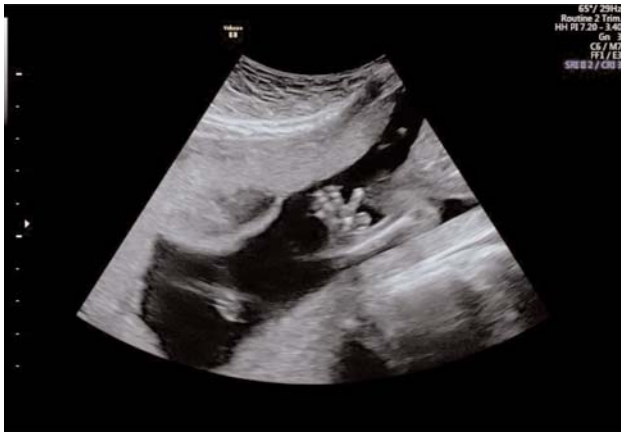

Fig. 1. Unilateral absence of ulna and radius.

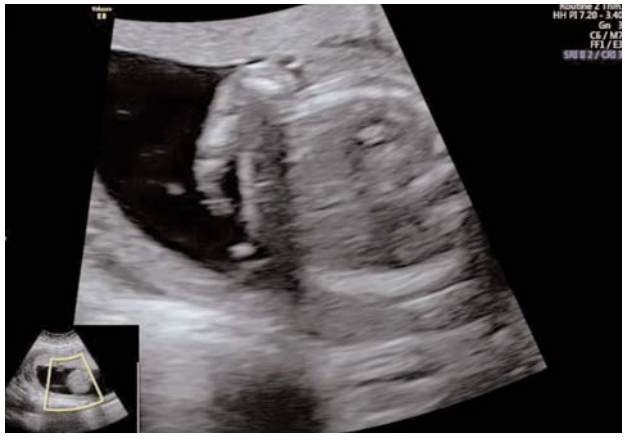

Fig. 2. Unilateral short humerus, ulna and radius.

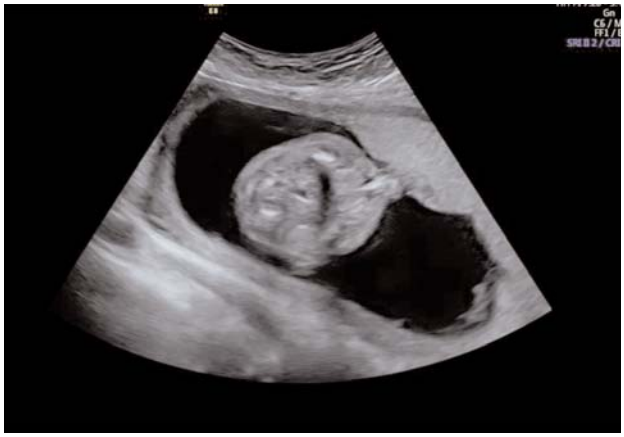

Fig. 3. Bilateral cleft palate and cleft lip.

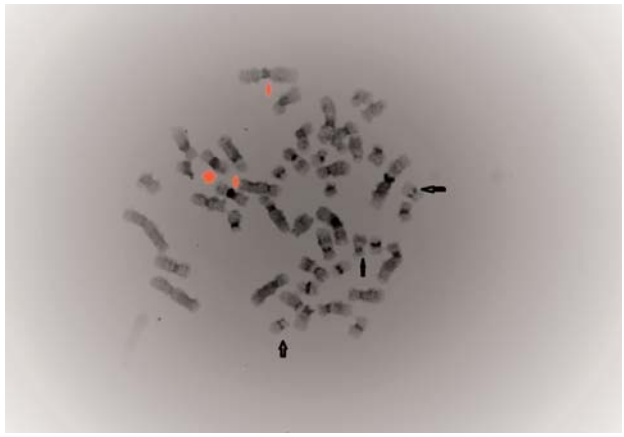

Fig. 4. Early centromere segregation (**black arrow**), and heterochromatic regions (**red arrow**).

Upon the pre-diagnosis of Roberts syndrome due to the ultrasonographic findings, the amniocentesis was performed for genetic investigation. When 40 chromosomes which were in metaphase stage were examined, 30 metaphases were found 46XY (normal male fetus), and aneuploidy was observed in 10 metaphases. In all metaphase evaluations, early centromere segregation and heterochromatin repulsion which are the characteristics findings for Roberts syndrome were observed (**Fig. 4**). The DNA obtained from the amniocytes was examined by polymerase chain reaction and direct sequencing of ESCO2 gene. Exon-specific primers were used for ESCO2 gene sequencing. Homozygous mutation c.1131+1G>A (g.16055 G>A) causing a change in the extension site was found in the sixth intron.

After detailed genetic consultation, the pregnancy was terminated at 19 weeks and 5 days of gestation. The family refused postnatal autopsy and magnetic resonance imaging. Postnatal physical examination was performed and defects in the long bones were found by X-ray imaging which were similar to the ultrasonographic findings found during prenatal period (**Fig. 5**).

The parents underwent genetic examination to evaluate the inheritance potential of ESCO2 gene in order to determine the risk of developing Roberts syndrome in future pregnancies. As a result of this examination, maternal and parental c.1131+1G>A heterozygote inheritance was found. The family was informed that there is a 25% chance for the recurrence of this syndrome in the future pregnancies due to the findings of this genetic examination.

Discussion

Roberts syndrome is a rare genetic disease with autosomal recessive inheritance pattern, leading to multiple congenital malformation. Although its prevalence and inheritance incidence are not known, there are about 150 cases reported in the literature.[4,5] Roberts syndrome is a genetic disease characterized with intrauterine and postnatal growth restriction, bilateral cleft palate and lip, craniofacial anomalies, bilateral symmetric tetraphocomelia or hypomelia (upper extremities are affected more than lower extremities), mental retardation and cardiovascular anomalies.

While extremity buds are observed at 8 weeks of gestation, extremity joints and fingers are observed by 11 weeks of gestation.[6] There are some case reports which found some findings specific to Roberts syn-

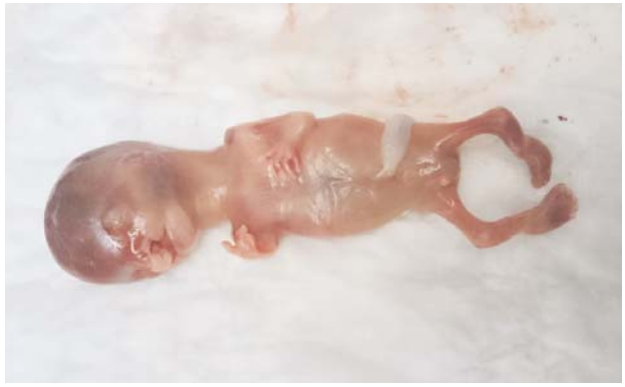

Fig. 5. Postnatal extremity contractures, bilateral cleft palate and cleft lip, and oligodactyly.

drome by prenatal ultrasonography and diagnosed during the early period in women with previous history of child(ren) with Roberts syndrome in their previous pregnancies.[2,7–11] In the diagnosis of Roberts syndrome, fetal face, genital organs, extremities, fingers and toes are the main structures to be checked. As cardiac anomaly prevalence is high in skeletal system anomalies, fetal echocardiography is an examination that should be carried out in all skeletal system anomalies.[12]

The diagnosis of Roberts syndrome is established by cytogenetic and molecular analyses. The findings of early centromere segregation and heterochromatin repulsion near centromere are the characteristic chromosomal anomalies seen in Roberts syndrome. In addition to these anomalies, random chromosomal loses and sporadic aneuploidies involving different chromosomes can be seen related with early centromere segregation.[11,13] However, normal karyotype is seen in some of the cases reported in the literature. The mutation in ESCO2 gene coding the protein which conducts the acetyl transferase activity necessary for the attachment of sister chromatids during S phase to each other is responsible for this syndrome.[7–9] Today, about 30 different mutations are known in ESCO2 gene causing Roberts syndrome, and phenotypic characteristics vary depending on the differences of these mutations.[14]

Hermann et al. identified SC phocomelia syndrome first in 1969, in which the courses of extremity defects, flexion contractures in joints, growth restriction and mental retardation are slow. This syndrome also develops in the pattern of autosomal recessive inheritance and with premature centromere segregation. Roberts syndrome and SC phocomelia syndrome are the diseases in the different spectrum of the defect in ESCO2 gene, where Roberts syndrome has a clinical course with severe findings and even results in intrauterine or postnatal death while SC phocomelia syndrome represents its slight form where individuals survive until their adulthoods.[15] Vega et al. found less cardiac defect in those with corneal opacity and more frequent mental retardation. They found skeletal deformity and cleft palate and lip together more frequently similar to our case. It was seen in the cases without cleft palate and lip that oligodactylia accompanied rarely.[14]

Roberts syndrome usually display familial inheritance. Our patient had the history of termination in her previous pregnancy upon the detection of phocomelia and bilateral cleft palate and lip. No genetic analysis was conducted for the reason of anomaly in the terminated pregnancy. When we found persistent left superior vena cava in the echocardiography, and bilateral shortness in upper and lower extremities, bone deficiency in the extremities with different degrees, bilateral oligodactylia, contracted lower extremities, cleft palate and lip and macropenis in the ultrasonographic anatomic screening in her current pregnancy, we considered Roberts syndrome first and conducted cytogenetic analysis by performing amniocentesis. We found out that the physical examination findings after termination were similar to the prenatal anomalies. In the karyotyping assessment that we evaluated 40 metaphases, we found karyotype as 46,XY and chromosomal anomaly in 10 metaphase assessment; however, the increases and decreases in chromosome numbers were not reiterative. Chromosomal aneuploidies related with early centromere segregation are seen frequently in Roberts syndrome, but these aneuploidies do not lead to different additional findings than the findings of Roberts syndrome as they are not the aneuploidy of the same chromosome in every cell and not the reiterating aneuploidies.[14]

We found the findings of early centromere segregation and heterochromatin repulsion in all metaphases. We obtained fetal DNA from amniocytes and we observed the mutation in ESCO2 gene by the direct sequencing of this DNA. We found homozygous mutation c.1131+1G>A (g.16055 G>A) causing a change in the extension site in the sixth intron. We found heterozygote mutation in ESCO2 gene in the maternal and paternal cytogenetic analysis. We recommended the family to have preimplantation genetic diagnosis or chorionic villus sampling for planned pregnancies in the future.

Conclusion

In conclusion, inappropriate preconceptional and prenatal care result in pregnancy with many chromosomal anomalies. The sonographic findings of many skeletal dysplasia conditions can be detected in the first trimester. If there is no family history, the genetic diagnosis of skeletal dysplasia conditions can be difficult. When skeletal dysplasia is detected and family requests termination, necessary consultation should be provided to the family after termination for detailed pathological

and radiological examinations. If family decides to continue pregnancy after prenatal diagnosis, the family should receive social and emotional support, and necessary precautions should be taken in order to provide sufficient care and support for the malformed baby during neonatal period. If genetic inheritance is found in family members for autosomal recessive diseases such as ESCO2 gene mutation, healthy embryos can be obtained by establishing preimplantation genetic diagnosis and the disease can be prevented to repeat.

Conflicts of Interest: No conflicts declared

References

1. Goh ESY, Li C, Horsburgh S, Kasai Y, Kolomietz E, Morel CF. The Roberts syndrome/SC phocomelia spectrum – a case report of an adult with review of the literature. Am J Med Genet A 2010;152A:472–8. [PubMed] [CrossRef]
2. Stioui S, Priviteria O, Brambati B, Zuliani G, Lalatta F, Simoni G. First-trimester prenatal diagnosis of Roberts syndrome. Prenat Diagn 1992;12:145–9. [PubMed] [CrossRef]
3. Zhou J, Yang X, Jin X, Jia Z, Lu H, Qi Z. Long-term survival after corrective surgeries in two patients with severe deformities due to Roberts syndrome: a case report and review of the literature. Exp Ther Med 2018;15:1702–11. [PubMed] [CrossRef]
4. Roberts JB. A child with double cleft of lip and palate, protrusion of the intermaxillary portion of the upper jaw and imperfect development of the bones of the four extremities. Ann Surg 1919:70:252–3.
5. Vega H, Gordillo M, Jabs EW. ESCO2 spectrum disorder. Roberts syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mefford HC, et al., editors. GeneReviews®. [Internet]. Seattle, WA: University of Washington. [updated 2013 November 14]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1153/ [PubMed]
6. Koskimies E, Lindfors N, Gissler M, Peltonen J, Nietosvaara Y. Congenital upper limb deficiencies and associated malformations in Finland: a population-based study. J Hand Surg Am 2011;36:1058–65. [PubMed] [CrossRef]
7. Otano L, Matayoshi T, Gadow EC. Roberts syndrome: first-trimester prenatal diagnosis. Prenat Diagn 1996:16:770–1. [PubMed] [CrossRef]
8. Feingold M. History of C-Patient with SC-Roberts/pseudothalidomide syndrome. Am J Med Genet 1992;43:898–9. [PubMed] [CrossRef]
9. Gruber A, Rabinerson D, Kaplan B, Ovadia Y. Prenatal diagnosis of Roberts syndrome. Prenat Diagn 1994;14:511–2. [PubMed] [CrossRef]
10. Benzacken B, Savary JB, Manouvrier S, Bucourt M, Gonzales J. Prenatal diagnosis of Roberts syndrome: two new cases. Prenat Diagn 1996;16:125–30. [PubMed] [CrossRef]
11. Schulz S, Gerloff C, Ledig S, Langer D, Volleth M, Shirneshan K, et al. Prenatal diagnosis of Roberts syndrome and detection of an ESCO2 frameshift mutation in a Pakistani family. Prenat Diagn 2008;28:42–5. [PubMed] [CrossRef]
12. Pajkrt E, Cicero S, Griffin DR, van Maarle MC, Chitty LS. Fetal forearm anomalies: prenatal diagnosis, associations and management strategy. Prenat Diagn 2012;32:1084–93. [PubMed] [CrossRef]
13. Sezer A, Kayhan G, Zenker M, Percin EF. Hypopigmented patches in Roberts/SC phocomelia syndrome ocur via aneuploidy susceptibility. Eur J Med Genet 2019;62:103608. [PubMed] [CrossRef]
14. Vega H, Trainer AH, Gordillo M, Crosier M, Kayserili H, Skovby F, et al. Phenotypic variability in 49 cases of ESCO2 mutations, including novel missense and codon deletion in the acetyltransferase domain, correlates with ESCO2 expression and establishes the clinical criteria for Roberts syndrome. J Med Genet 2009;47:30–7. [PubMed] [CrossRef]
15. Herrmann J, Feingold M, Tuffli G, Opitz J. A familial dysmorphogenetic syndrome of limb deformities, characteristic facial appearance and associated anomalies: The "pseudothalidomide"' or "SC syndrome". Birth Defects Orig Artic Ser 1969;5:81–9.