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Kranioraşizis Vakalarının Değerlendirilmesi

EVALUATION OF THE CASES OF CRANIORACHISCHISIS

ERDAL ŞEKER [1] Orcid ID: 0000-0001-9818-0414
MUSTAFA KOÇAR [1] Orcid ID: 0000-0001-5350-7233
COŞKUN ÜMİT [1] Orcid ID: 0000-0003-1694-0649
HASAN SÜT [1] Orcid ID: 0000-0003-0982-3356
KORAY GÖRKEM SAÇINTI [1] Orcid ID: 0000-0003-0982-3356
GÜLŞAH AYNAOĞLU YİLDİZ [1] Orcid ID: 0000-0002-3283-7783
ESRA ÖZKAVUKÇU [2] Orcid ID: 0000-0002-2202-7760
ACAR KOÇ [1] Orcid ID: 0000-0003-2482-7478

[1] Department of Obstetrics and Gynecology, Ankara University School of Medicine, Ankara, Turkey
[2] Department of Radiology, Ankara University School of Medicine, Ankara, Turkey

ÖZ

Amaç: Kranioraşizisis, nöral tüp defektlerinin (NTD'ler) nadir görülen ve ciddi bir varyantıdır. Her 10.000 gebelikten 0.51'inde görülür. Bu fetal anormallik için bildirilen bir etiyoloji yoktur.

Gereç ve yöntemler: 13 yılı aşkın veriler retrospektif olarak elde edildi. Çalışmaya Kranioraşizisis tanısı konulan ve nekroskopi ile kesin tanıları netleşen fetüsler çalışmaya alındı.

Bulgular: Kliniğimizde son 13 yılda kranioraşizisis tanısı konulan ve nekroskopi ile kesin tanısı netleşen altı olguyu sunuyoruz. Kranioraşizisis, başlı başına ciddi bir anomali olması ve diğer anormalliklere eşlik etme oranının yüksek olması nedeniyle halen hayati bir anomalidir.

Sonuç: Kranioraşizisis ilk trimesterde teşhis edilebilir. Eksensefali tanısı alan hastalarda özellikle vertebral kolon incelenmelidir. Kranioraşizisis tanısı konduğunda kalp, ekstremiteler ve torasik karın dikkatle incelenmelidir. Eşlik eden diğer anomalilerin oranı yüksektir. İleride yapılacak araştırmalarda kranioraşizisin nedeninin anlaşılması bu anomaliye eşlik eden diğerlerinin de nedeninin anlaşılmasını sağlayacaktır.

Anahtar kelimeler: Kranioraşizisis, Nöral tüp defekti, Prenatal tanı, Fetal anomali

ABSTRACT

Objective: Craniorachischisis is a rare and severe variant of neural tube defects (NTDs). It occurs in 0.51 of every 10,000 pregnancies. There is no reported etiology for this fetal abnormality.

Material and methods: Over 13 years data was obtained retrospectively. Fetuses diagnosed to have craniorachischisis whose definite diagnoses were clarified by necroscopy were enrolled in the study.

Results: We present six cases diagnosed with Craniorachischisis in our clinic in the last 13 years, whose definitive diagnosis was clarified by necroscopy. Craniorachischisis is still a vital anomaly because it is a severe anomaly itself and the rate of accompanying other abnormalities is high. Fully elucidating the cause can also be a guide for others.

Conclusion: Craniorachischisis can be diagnosed in the first trimester. The vertebral column should especially be examined in patients diagnosed with exencephaly. The heart, extremities, and thoracic-abdomen should be carefully examined when craniorachischisis is diagnosed. The rate of other anomalies accompanying is high. In future research, if the cause of craniorachischisis is understood, it will provide an understanding of the cause of other accompanying this anomaly.

Keywords: Craniorachischisis, Neural tube defects, Prenatal diagnosis, Fetal anomaly

Sorumlu Yazar/ Corresponding Author: Erdal Şeker
Adres: Balkiraz, Aü Tıp Fakültesi Hst., 06100 Mamak/Ankara 06100 Mamak - Türkiye
E-mail: erdalseker84@gmail.com

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INTRODUCTION

Neural tube defects (NTDs) are the second most common congenital anomalies (1). NTDs contain central nervous system anomalies and spinal cord defects. Anencephaly, acrania, and spina bifida are the most common variants. NTDs can be caused by genetic or teratogenic factors in the third and fourth weeks of embryonic development. NTDs can also be caused by drugs that impair folic acid metabolism, diabetes mellitus (DM), and hyperthermia This existing anomaly, whose specific cause is unknown, is accompanied by an extremely high frequency of other anomalies. (1, 2)

Craniorachischisis is a rare and severe form of NTD and coexists with exencephaly and spina bifida (3). Malformations of the ectoderm and mesoderm induce craniorachischisis. Johnson et al. reported that craniorachischisis was detected in 0.51 of 10,000 pregnancies (2). This existing anomaly, whose specific cause is unknown, is accompanied by an extremely high frequency of other anomalies.

With the widespread use of antenatal USG, it can be diagnosed in the first trimester. We aimed to present the necroscopic findings, genetic results and ultrasound markers of craniorachischisis cases in our clinic.

MATERİAL AND METHOD

All singleton pregnancies delivered in the Obstetrics and Gynecology Department of Ankara University, School of Medicine, between 2008 and 2021 were investigated in a retrospective study. Pre-examination ultrasound settings were made in accordance with ISUOG recommendations. (4) Consent for using data was obtained for this retrospective study.

We included cases of craniorachisis confirmed by postnatal examination. We excluded only cases of NTD or acrania.

Ethics committee approval was obtained. (Ethics committee approval number: 2021/486 Date: 12.01.2022) The study was conducted under the Declaration of Helsinki. Misoprostol was used for pregnancy termination. FİGO recommendation was used for misoprostol dose and frequency.(5) To prevent neural tube defects, high-dose folic acid replacement was recommended before their next pregnancy.

Statistical analysis

Statistical analysis was not conducted in this article.

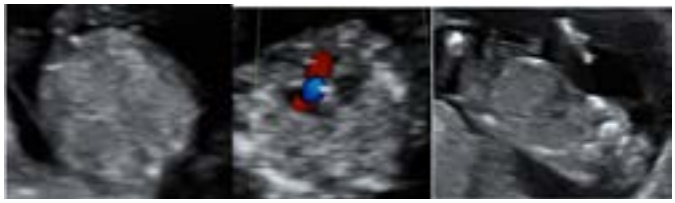
RESULTS

A total of 6 cases with craniorachischisis were reached.

Case 1

A 27-year-old, G1P0 patient was admitted to our hospital at 13 weeks of gestation. There was an unremarkable medical history and family history and no history of drugs or substance abuse. Cranial bone was not observed in the first-trimester ultrasound. It was also found that the vertebral column was split and the left ventricle of the heart was not filled with Doppler flow. Hypoplastic left heart (HLHS) with accompanying Craniorachischisis was considered as a preliminary diagnosis. The parents were informed about the prognosis, and the fetus was terminated. Craniorachischisis diagnosis was confirmed (Figure 1). Due to parental refusal, necroscopy was not performed, and the diagnosis of HLHS could not be verified.

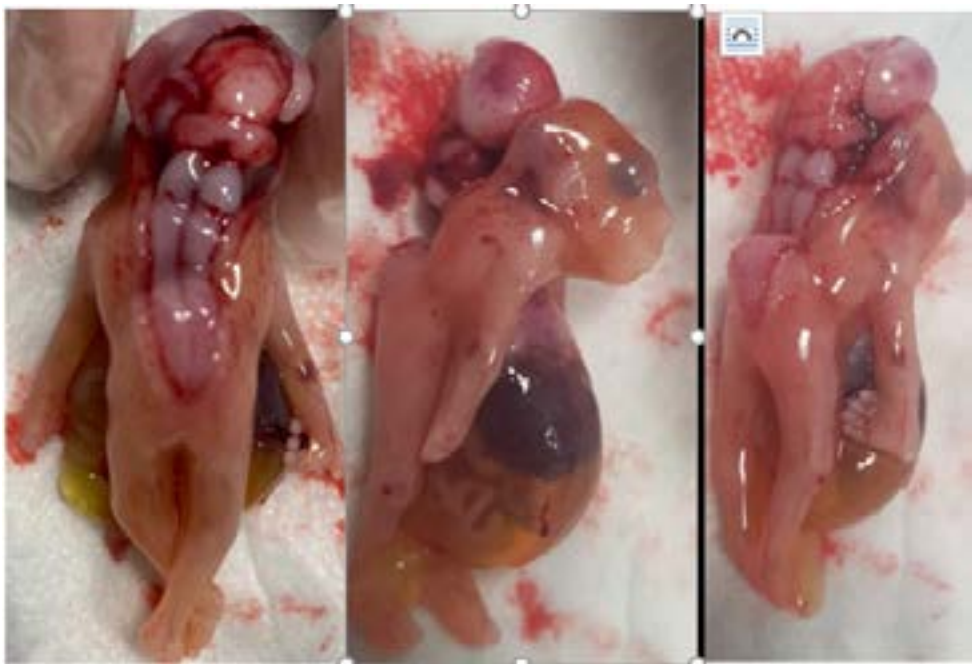
Figure-1: Craniorachisisis with HLHS Figure-1: Craniorachisisis with HLHS



Case 2

A 37-year-old, G5P4 patient was admitted to our hospital at 15 weeks of gestation. There was an unremarkable medical history and family history and no history of drugs or substance abuse. There was no cranial bone in the first-trimester screening. There was no integrity found in the vertebral column. A defect starting from the sternal region and extending to the under umbilicus covering with a pouch was observed in the anterior thorax. The fetal lung, heart, intestine, and liver were herniated into the sac (thoracic-abdominoschisis). Radial agenesis and flexion deformity in the hands were observed. Genetic analysis and termination were recommended for the patient. The fetus was terminated. The external examination revealed a defect (craniorachischisis) extending from the posterior of the cranium to the vertebral column. Anterior thoracic-abdominoschisis, including lung, heart, liver, and intestines in the pouch was confirmed (Figure-2). The karyotype analysis reported Trisomy 18.

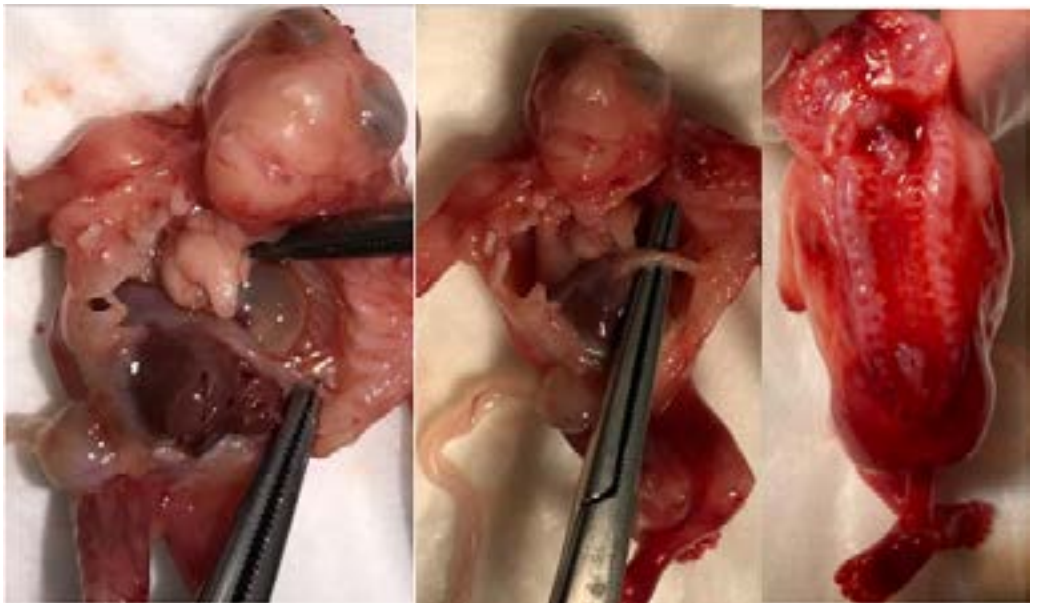
Figure-2: Craniorachisisis with thoraco-abdominoschisis and radius agenesia



Case 3

A 38 year-old, G5P4 pregnant was admitted to our hospital at 13 weeks of gestation. There was an unremarkable medical history and family history and no history of drugs or substance abuse. The fetal cranium was not observed in the first-trimester ultrasound. The brain tissues were observed directly related to the amnion cavity, and as cystic structures. The orbital structures were in order and a typical Mickey-Mouse sign was observed. On the following examination demonstrated that the fetal vertebral structures were separate. Subsequently, in the segment where the heart was evaluated, there was a cystic appearance on the left side of the heart. It was assessed as gastric herniation due to the diaphragmatic hernia. Following the examination findings, the family was informed about the prognosis of the fetus. Amniocentesis (AS) was applied to the patient for genetic analysis. Subsequently, the termination procedure was performed on the patient with the family's consent. During the examination, the spinal cord was exposed from the occipital to caudal regions (Craniorachischisis). The cranial bone was not observed, and the neural tissues were visible from the exterior (Exencephaly). The necroscopy procedure was then initiated. The left lobe of the liver and stomach were herniated into the left thorax after the incision. The fetal heart was observed to be dextroposed with a rightward deviation, and the herniated lobe of the liver and hypoplastic lung (Figure-3.) The karyotype analysis reported 46 XY.

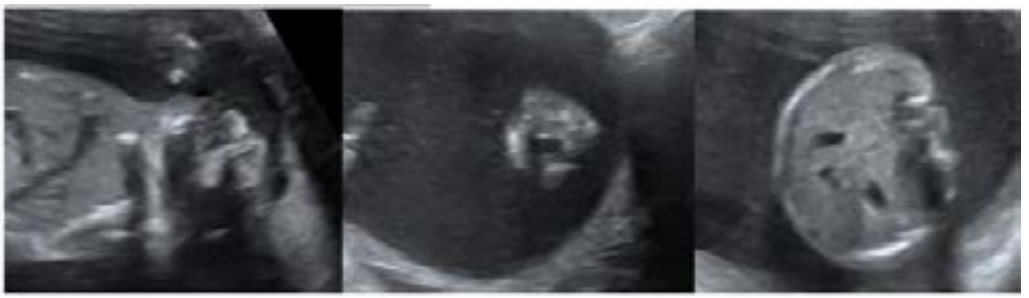
Figure-3: Craniorachisisis with congenital diaphragmatic hernia



Case 4

A 21-year-old, G1P0 patient was admitted to our hospital at 15 weeks of gestation. She had insulin-dependent gestational diabetes mellitus. Ultrasound examination detected that one fetus of the twin pregnancy had exencephaly, cleft lip-palate, spina bifida, and bilateral pes equinovarus. She did not accept genetic screening or termination of the pregnancy. She underwent a cesarean section at 31 weeks of gestation due to active preterm labor. The malformed fetus died after birth. The parents refused to necroscopy (Figure-4).

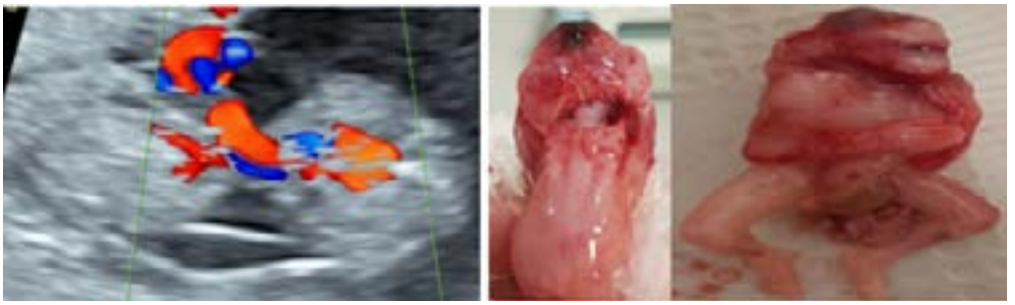
Figure-4: Craniorachisisis with cleft lip



Case 5

A 23-year-old, G1P0 patient was admitted to our hospital at 13 weeks of gestation. There was an unremarkable medical history and family history and no history of drugs or substance abuse. Cranial bone was not observed performed in the first-trimester ultrasound. In addition, the vertebral column was found to be split. On the ultrasonography, an omphalocele is diagnosed when a fetal anterior midline mass composed of abdominal contents that have herniated through a central midline defect at the base of the umbilical insertion is observed. The family was informed, and termination was performed. Craniorachischisis and omphalocele were diagnosed following termination. The karyotype analysis revealed a normal karyotype, and the MTFHR gene was identified as a homozygous mutant (Figure-5).

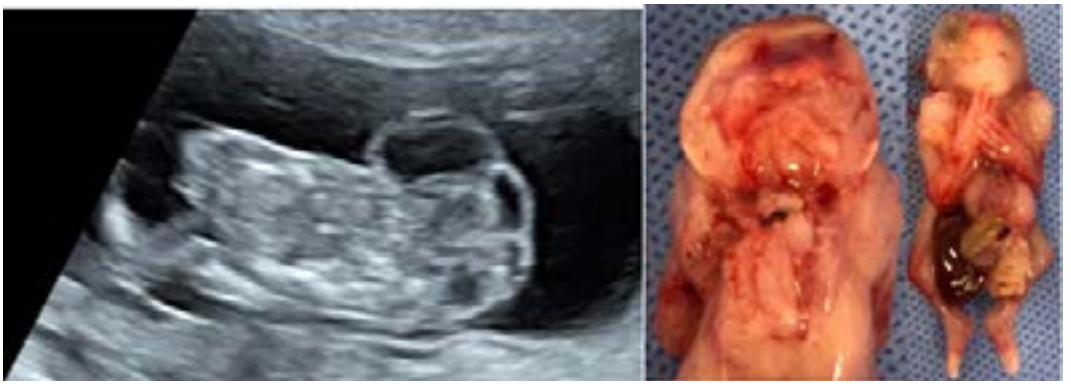
Figure-5: Craniorachisisis with omphalocele



Case 6

A 21-year-old, G1P0 patient was admitted to our hospital at 13 weeks of gestation. There was an unremarkable medical history and family history and no history of drugs or substance abuse. As the cranium bone was not visible during the first-trimester

Figure-6: Craniorachisisis with thoraco-abdominoschisis



A 21-year-old, G1P0 patient was admitted to our hospital at 13 weeks of gestation. There was an unremarkable medical history and family history and no history of drugs or substance abuse. As the cranium bone was not visible during the first-trimester ultrasound. There was no cranial bone detected during the USG. The vertebral column was observed to be devoid of integrity. In the anterior thorax, a defect extending from the sternal region to the under umbilicus was noted. A pouch concealed these defects. Lung, heart, intestine, and liver were reported to have herniated into the sac (thoracic-abdominoschisis). Genetic counseling and termination were advised for the patient. The pregnancy was terminated. The external examination revealed a defect (craniorachischisis) extending from the posterior of the skull to the vertebral region. The presence of an anterior thoracoabdominal sac was confirmed. Intestines, lungs, heart, and liver were observed in the pouch. The result of the karyotype analysis was normal (Figure-6)I

DISCUSSION

There are multiple causes of NTD, including medications, medical conditions, and genetic defects (6). Antiepileptic drugs that affect folic acid metabolism and the mother's exposure to hyperthermia in the first trimester may also cause NTDs (7).

Neuroepithelial cells differentiate to form the neural tube three to four weeks after fertilization. The neural tube begins to close in the cervical region and progresses to the cranial and caudal regions. Due to the difficulty of this process, cranial closure problems may result in anencephaly, while caudal closure problems may result in spina bifida and/or meningomyelocele.

The frequency of NTD varies by region, with an average of 3.40 per 10,000 live births and 4.41 per 10,000 live births, stillbirths, or terminations. (2, 4, 6) It can be isolated or maybe a component of other syndromes. While termination is an option for a component such as an acrania, prenatal and postnatal treatment are possible for spina bifida, particularly intrauterine treatment. The NTD etiology is multifactorial. It may be caused by genetics, or it may be isolated or accompanying other anomalies, and also related to folic acid deficiency or folic acid metabolism disorder.

The cases of Craniorachischisis have been reported to be accompanied by various syndromes. There are cases associated with chromosomal abnormalities such as trisomy 18 and trisomy 11, publications stating that Craniorachischisis cases accompany pentalogy of Cantrell, and publications stating that they are accompanied by syringomyelia and iniencephaly (8, 9, 10, 11, 12).

In the first reported case, HLHS is associated with Craniorachischisis (Figure 1). According to our best knowledge, this association has not previously been described in the literature, and our case will be the first to demonstrate it. The rate of HLHS associated with genetic anomalies is low, at approximately 14% (12). In a 2017 study conducted on mice and zebrafish, the SAP130 and PCDHA13 genes were found to be associated with HLHS (13). Future research could shed light on the etiology of craniorachischisis.

In the trisomy 18 case of Donaldson et al., both Craniorachischisis and thoracic-abdominal schisis were detected (14). These findings are comparable to our patients in the second and sixth cases (Figure 2). Trisomy 18 was detected in our second case as well. While our second patient had bilateral radius agenesis, Donaldson was diagnosed with rocker bottom and camptodactyly. In studies conducted on mice, AP-2 mutations were associated with cranial and abdominal anomalies (15). Regarding this gene, which is located on chromosome 6 in mice, little is known about its counterpart in humans or Trisomy-18. However, in our fifth case, only an omphalocele sac was present, and this patient's karyotype was reported as normal.

The third case had CDH detected on the ultrasonography and confirmed by necroscopy. (Figure-3) 40% of CDH cases are not isolated and are accompanied by other anomalies. There is no cytogenetic anomaly specific to CDH, and additional anomalies can be found with comparative genomic hybridization as an extra (16). Also, Singh et al. described an atypical form of Fryns syndrome in a case reported earlier (17). Due to our patient's early pregnancy, it was challenging to identify facial anomalies. Additionally, there were diaphragmatic hernia and pulmonary hypoplasia, which are other components. In addition, genes cannot be studied in our genetic center. Consequently, we could not study the PIGN gene mutation causing Fryns syndrome (16). Therefore, we believe that if a definitive diagnosis of Fryns syndrome could be made, the components required for early diagnosis could change. The demographic characteristics of the cases are shown in Table 1.

In our 4th case, cleft lip is present. In the literature, there is only a case similar to our case, but unlike ours, in that case, severe gastrointestinal and lung anomalies are also accompanied (17).

Craniorachischisis is still a significant anomaly because it is a

severe anomaly and the rate of accompanying other anomalies is high. Fully elucidating the cause can also be a guide for other anomalies. Frequently, there are multicenter case reports of Craniorachischisis in the literature. However, our case series consist of a single center.

The limitation of our study is that it was a single-center and retrospective study, and we could not do sufficient genetic studies. The strength of our study is the confirmation of the cases with postnatal findings and necroscopic examination. It is also important that one of our cases is with HLHS which has never been reported before. The three cases we reported, were not isolated and accompanied by other anomalies.

CONCLUSION

We think that with the increase of awareness of craniorachischisis, the diagnosis rate may increase with careful prenatal USG screening. We also think that necroscopy and genetic evaluations will contribute to the literature.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Acknowledgments

None

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