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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Retrospective Analysis of Fetal Central Nervous System Anomalies Diagnosed Prenatally in a Tertiary Center

Tersiyer Merkezde Prenatal Tanı Alan Fetal Santral Sinir Sistemi Anomalilerinin Retrospektif Analizi

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Abstract

Objective: In our study, we aimed to emphasize the prevalence and characteristics of central nervous system (CNS) anomalies detected by fetal ultrasonography in normal and high-risk pregnant women admitted to our clinic.

Methods: In this retrospective analysis, cases who applied to University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Perinatology Clinic between January 1, 2017 and January 1, 2021 and who were found to have CNS anomaly were included. The data of 81,163 pregnant women were analyzed. CNS anomaly was detected in 712 pregnant women.

Results: When all cases included in our study were examined, the median maternal age was calculated as 27.4 and the median of gestational weeks as 21.9. The median gravidas of the pregnant women were 2.4, and the median of the parities was 1.1. When all diagnoses were examined, ventriculomegaly (n=217, 30%) was the most common anomaly among the CNS anomalies. The second most common anomaly we detected was the cases of neural tube defect (n=95, 13.17%).

Conclusion: Termination option could not be offered to families for anomalies incompatible with life in pregnant women whose gestational weeks are more than 24 weeks. Some of the families who were offered the termination option did not accept the termination option due to cultural reasons and religious beliefs. For this reason, early diagnosis becomes important in the perinatal period in order to present this option to the family.

Keywords: Anomaly, ventriculomegaly, central nervous system, neural tube defects

Öz

Amaç: Çalışmamızda kliniğimize başvuran normal ve yüksek riskli gebelerde fetal ultrasonografi ile tespit edilen santral sinir sistemi (SSS) anomalilerinin görülme sıklığı, özelliklerinin vurgulanması amaçlamıştır.

Yöntem: Retrospektif olarak yapılan bu analize, 1 Ocak 2017-1 Ocak 2021 yılları arasında Sağlık Bilimleri Üniversitesi, İzmir Tepecik Eğitim ve Araştırma Hastanesi Perinatoloji Polikliniği'ne başvuran ve SSS anomalisi saptanmış olgular dahil edildi. 81.163 gebenin verileri değerlendirildi. Yedi yüz on iki gebede SSS anomalisi tespit edildi.

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Öz

Bulgular: Çalışmamıza dahil edilen tüm olgular incelendiğinde anne yaşı ortancası 27,4, gebelik haftaları ortancası 21,9 olarak hesaplandı. Gebelerin gravidaları ortancası 2,4, paritelerin ortancası 1,1 olarak bulunmuştur. Tüm tanılar incelendiğinde SSS anomalileri içinde ventrikülomegali (n=217 %30) en sık tespit edilen anomali olmuştur. İkinci en sık tespit ettiğimiz anomali nöral tüp defekti (n=95 %13,17) olguları olmuştur.

Sonuç: Anomali taranması amacı ile hastanemize başvuran gebelerin gebelik haftalarının ileri olması sebebi ile yaşamla bağdaşmayan anomaliler için terminasyon seçeneği ailelere sunulamamıştır. Terminasyon seçeneği sunulan ailelerin bir kısmı da kültürel sebepler ve dini inançlar sebebi ile terminasyon seçeneğini kabul etmemiştir. Bu sebeple bu seçeneğin aileye sunulabilmesi için perinatal dönemde erken tanı önem kazanmaktadır.

Anahtar Kelimeler: Anomali, ventrikülomegali, santral sinir sistemi, nöral tüp defektleri

Introduction

Ultrasonography (USG) is an important diagnostic tool that we use in our daily routine to examine the development and anatomical structures of the fetus and to detect structural anomalies. During fetal development, the development of organ structures in the body occurs at different times for each organ. With USG, we determine whether the anatomical structures are normal or not by making detailed examinations in certain weeks. Although the most appropriate time interval for performing these detailed scans is between the 18th and 20th weeks of pregnancy, some anomalies can be detected in the earlier weeks. The benefits of early fetal USG performed at 11th and 14th weeks are that the cranial bones are thin and the brain can be evaluated from all angles, especially with transvaginal USG. As the gestational week progresses, it becomes difficult to evaluate intracranial structures due to the increase in cranial ossification[1].

Structural anomalies of the fetus are seen in 2-3% of all pregnancies[2]. One of the most common groups in fetal anomalies is central nervous system (CNS) anomalies. CNS anomalies are the most common anomalies after cardiovascular system anomalies. It has been reported that CNS anomalies are seen at a rate of 1.4-1.6 per 1000 live births[3]. It constitutes approximately 30% of the anomalies detected in the perinatal period[4]. The earliest anomaly detected in the CNS is acrania[5]. It can turn into anencephaly with the sequence of acrania-exencephaly-anencephaly. The brain tissue cannot be protected and is gradually destroyed by exposure to the harmful effects of amniotic fluid and mechanical injuries[6]. With the progression of the gestational week, anomalies such as spina bifida and hydrocephalus follow. It should be kept in mind that some anomalies can be detected even later than routine detailed screening.

The approach to a pregnant woman who did not have any features in her previous pregnancy and a pregnant woman with a history of congenital anomaly should be examined differently. CNS anomalies can be seen alone or may accompany any syndrome[4]. For this reason, if CNS anomaly is detected in a pregnant woman, detailed USG and karyotype analysis should also be performed.

While the most common cranial anomaly is ventriculomegaly, other major anomalies that can be seen in the CNS can be listed as: neural tube defects (NTD), holoprosencephaly, posterior fossa anomalies (Dandy-Walker complex, etc.), callosal agenesis and vascular malformations.

Since CNS anomalies have high mortality and morbidity rates in the fetus, early diagnosis becomes important. If the diagnosis is a malformation incompatible with life, the family may be offered the option of termination. With prenatal genetic counseling services, families can choose to terminate the pregnancy when the poor prognosis is explained in a way that the family can understand.

In this study, we aimed to share our experiences with CNS anomalies detected in our clinic.

Materials and Methods

The cases who were evaluated in the Perinatology Clinic of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital for high-risk pregnancy between 1 January 2017 and 1 January 2021 and found to have a CNS anomaly in the fetus were included in the study. The data were retrospectively analyzed and recorded from the hospital digital recording system and patient files. Descriptive statistics were primarily examined in the study. The statistical package for the Social Sciences (SPSS) 20 program was used in the analysis of the data. Variables were expressed in n (frequency) and percentage (%). This study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee (20201/02-02, 22/02/2021).

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences 20 programs. Variables were expressed in n (frequency) and percentage (%).

Results

In our study, data of 81,163 pregnant women who applied to our perinatology clinic were analyzed. Among these patients, 712 (0.88%) pregnant women with CNS anomaly were detected by fetal USG. When all cases included in our study were examined, the maternal age ranged from 14 to 47, with an average of 27.4, weeks of gestation ranging between 10 and 39, with an average of 21.9. The gravidas of the mothers ranged from 1 to 11, with an average of 2.4 and the average of parities as 1.1 (Table 1).

In our study, the anomaly types were examined in 10 subgroups, and ventriculomegaly (30%) was the most common CNS anomaly. Subsequently, midline developmental anomalies (16.9%), posterior fossa anomalies (16.5%) and vertebral anomalies (16.5%) were detected (Graphic 1).

When considered independently from the groups, ventriculomegaly (n=217, 30%) was the most common anomaly among the CNS anomalies. The second most common anomaly we found was NTD (n=95% 13.17). These were followed by anencephaly cases (8.7%) and corpus callosum agenesis (8.04%) (Table 2).

Discussion

One of the most important anomalies detected in perinatal follow-up is CNS anomalies[7]. Detection of these anomalies is very important in terms of the course of pregnancy. According to the anomaly detected, the path to be followed is determined according to the underlying cause, the course of the pregnancy, and whether it is compatible with life or not. The most common method used in fetal screening is USG[8]. Apart from this, fetal magnetic resonance is also used, since USG is insufficient for various reasons in detecting CNS anomalies. We evaluated the anomalies detected in our study with fetal USG.

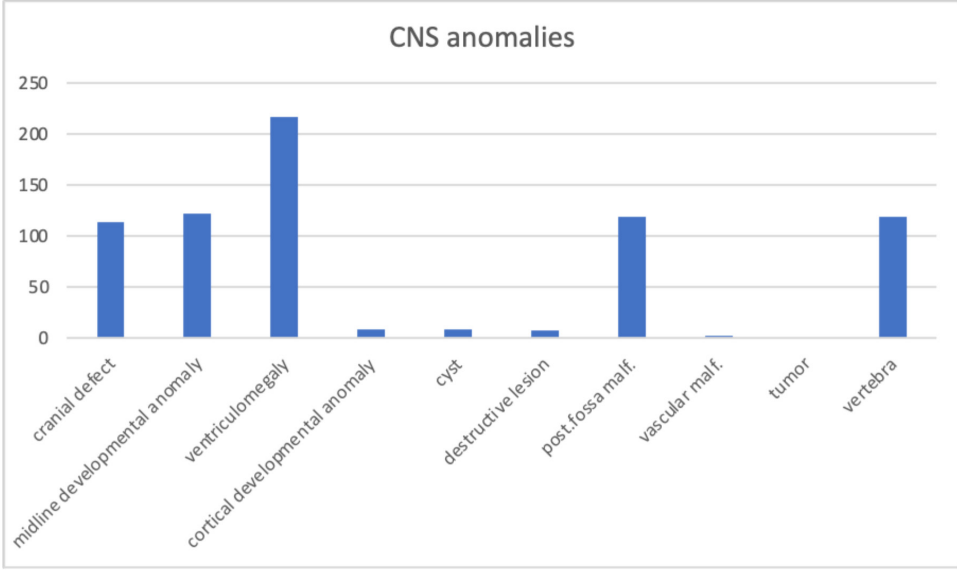
Table 1. Demographic characteristics of the patients

	Minimum	Maximum	Mean
Age	14	47	27.4
Gravida	1	11	2.4
Parity	0	8	1.1
Pregnancy week	10	39	21.9

In addition to USG, various markers are also used in the detection of anomalies. Alpha fetoprotein (AFP) is a plasma protein found in amniotic fluid. When there is a skin defect, the concentration of this plasma protein in the amniotic fluid increases. We can detect anomalies such as NTD by measuring maternal serum concentration of AFP and examining with fetal USG. AFP is useful in detecting only open NTD[9]. The use of USG in the perinatal diagnosis of NTD has become

Table 2. Distribution of patients according to anomaly types

Cranial defects	Anencephaly	63
	Akalvaria	3
	Exencephaly	5
	Encephalocele	22
	Acrania	21
Medium line developmental anomalies	Corpus Callosum Agenesis	58
	Atelencephaly/Aprosencephaly	6
	Alobar Holoprosencephaly	50
	Lobar Holoprosencephaly	4
	Semilobar Holoprosencephaly	1
	Septooptic Dysplasia	1
	Sintencephaly	2
Ventriculomegali		217
Cortical developmental anomalies	Schizencephaly	7
	Lysencephaly	1
	Polymicrogyria	1
Cysts	Arachnoid Cyst	7
	Glioependymal Cyst	2
Destructive lesions	Intracranial Bleeding	8
Posterior fossa malformations	Chiari Type 2	28
	Aquaductus Stenosis	17
	Dandy Walker Malformation	7
	Vermian Agenesis	11
	Blake Pouch Cyst	9
	Mega Sisterna Magna	28
	Cerebellum Hypoplasia	15
	Rhombencephalosnapsis	2
	Walker-Walburg Sendrome	2
Vessel malformation	Galen's New Malformation	3
Tumors	Parenchymal Brain Tumors	1
Vertebra	Neural Tube Defects	95
	Tethered Cord	5
	Iniencephaly	2
	Diastometomelia	4
	Sacrococcygeal Teratoma	13



Graphic 1. Distribution of the cases by subgroups

CNS: Central nervous system

a routine procedure. It has become a routine screening examination due to its effectiveness, availability and low cost, and AFP is not used except in very necessary cases.

In order to prevent NTD, it is recommended to give 0.4 mg of folic acid supplement daily to every woman of childbearing age[10]. However, since most pregnancies occur unplanned, the benefits of folic acid in pregnancy are limited.

The most common CNS anomalies in the studies in the literature differ. While NTD was found most frequently in some studies, ventriculomegaly was seen to be the most frequently detected CNS anomaly in some studies. In the study conducted by Adama van Scheltema et al.[4], NTD was detected with a rate of 51%, while ventriculomegaly/ hydrocephalus was found in the second frequency with a rate of 26%. In a study conducted by Domröse et al.[11], Hydrocephalus (45%) was found to be the most common CNS anomaly. In another study, NTD (38%) was found to be the most frequently detected CNS anomaly[12]. In another study, ventriculomegaly was found the most common with a rate of 44.9%[13]. In a study conducted by Hadzagić-Catibusić et al.[10], NTD was the most common at a rate of 38.6%. In our study, we found ventriculomegaly at a rate of 30% as the most common anomaly. In the second frequency, 13.17% NTD cases were detected. In most of the literature studies, it is observed that the most common CNS anomaly is NTD. Our rates are lower than the literature. We attribute this to the high number of cases we scanned.

Cranial ossification begins to occur in the 11th gestational week[14]. Acrania is one of the anomalies that can be detected at the earliest period with USG. Acrania forms first, and then it turns into exencephaly with the degeneration of the cerebral hemispheres. Finally, it turns into anencephaly[15]. We found the rate of acrania as 2.91% (n=21). When the gestational weeks of our cases included in our study are examined, it is observed that most of them applied to our clinic in the last weeks of gestation. For this reason, cases of acrania can be considered to be the precursor of anencephaly cases. Coşar et al.[16] found encephalocele in 21.7% and anencephaly in 8.7% of pregnant women with NTD in their study.

Holoprosencephaly is a midline developmental anomaly that develops as a result of failure to decompose brain structures during the formation of forebrain structures. Midline developmental anomalies (16.9%) are the second most frequently detected anomalies among the subgroups in our study. The incidence of holoprosencephaly in live births is 1 in 16,000 live births[17]. Alobar holoprosencephaly is the 5th most common anomaly detected in our study with a rate of 6.93%.

Corpus callosum agenesis is the 4th most common anomaly in our study with a rate of 8.04%. It is seen 1-3 in every 1000 births. Hadzagić-Catibusić et al.[10] detected corpus callosum agenesis at a rate of 7.9% in their study. In the literature, it can be seen alone or together with chromosomal and congenital anomalies. Our frequency of detecting corpus

callosum agenesis is compatible with the literature, although we could not show the presence of accompanying anomalies since we considered the anomalies we detected in our study one by one.

Since CNS anomalies may be accompanied by other anomalies, karyotype analysis was deemed appropriate. Since very few patients in our study agreed to have karyotype analysis, the details were not included. In addition, the fact that the study is a retrospective study has limited us in terms of generalizing and classifying the results.

Both environmental and genetic factors play a role in CNS anomalies. Diabetes mellitus is an important risk factor for CNS anomalies. Pregnancy over 35 years of age, multiple pregnancy, fetal alcoholism, polyhydramnios, oligohydramnios are other important risk factors. In NTDs, the highest risk in terms of age is under 20 and over 35 years old. Influenza virus, Cytomegalovirus, Rubella virus, Varicella-zoster virus, Toxoplasma gondi during pregnancy are risk factors for CNS anomalies[6]. Since CNS anomalies can have a mortal course, early diagnosis is important. It will help to distinguish curable defects and avoid wrong decisions about anomalies that should not be terminated[18]. Different anomalies may occur by being exposed to the same active substances at different weeks of gestation. Determining the risk factors and determining the underlying anomaly is important in terms of the course of pregnancy.

Study Limitations

Our study included some limitations. One of the biggest deficiencies of our study is that we could not compare the anomalies we detected with the postpartum results. The refusal of the families for whom the termination of pregnancy recommended due to fetal major CNS anomalies, and the inability to perform a postmortem examination in families who accepted termination limited the effectiveness of the study.

Conclusion

Since CNS anomalies can be alone or accompany other system anomalies, a detailed screening of all organs should be made. Since CNS anomalies often appear together with chromosomal anomalies, karyotype analysis should also be performed. Because families have concerns about whether to continue pregnancy or not, depending on the severity of the type of anomaly, they need detailed information about the process they will experience after birth. Termination option for anomalies incompatible with life should be presented to the family in an impartial manner, respectful to the socioeconomic level/culture/beliefs of the family, and the follow-up/treatment of those compatible with life should be explained to the family. With more comprehensive studies examining each country or ethnic origin, it can be determined whether there are differences between communities and ethnic origins and whether the cases have changed their management.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee (20201/02-02, date: 22.02.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.Ö., H.G., E.U., B.S., H.G.P., Design: İ.Ö., H.G., E.U., B.S., H.G.P., Data Collection or Processing: İ.Ö., H.G., E.U., B.S., H.G.P., Analysis or Interpretation: İ.Ö., H.G., E.U., B.S., H.G.P., Literature Search: İ.Ö., H.G., E.U., B.S., H.G.P., Writing: İ.Ö., H.G., E.U., B.S., H.G.P.

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References

1. Malinger G, Paladini D, Haratz KK, Monteagudo A, Pilu GL, Timor-Tritsch IE. ISUOG Practice Guidelines (updated): sonographic examination of the fetal central nervous system. Part 1: performance of screening examination and indications for targeted neurosonography. Ultrasound Obstet Gynecol 2020;56:476-84.
2. Rydberg C, Tunon K. Detection of fetal abnormalitiesby second-trimestre ultrasound screening in a non-selected population. Acta Obstet Gynecol Scand 2017;96:176-82.
3. Chitty LS, Pilu G. The challenge of imaging the fetal central nervous system: an aid to prenatal diagnosis, management and prognosis. Prenat Diagn 2009;29:301-2.
4. Adama van Scheltema PN, Nagel HT, Brouwer OF, Vandenbussche FP. Outcome of children with prenatally diagnosed central nervous system malformations. Ultrasound Obstet Gynecol 2003;21:41-7.
5. Chervenak FA, Isaacson GC, Campbell S. Anomalies of the cranium and its contents. In Ultrasound in obstetrics and gynecology. In: Chervenak FA, Isaacson GC, Campbell S, editors. Little Brown and Company, Boston, 1993. p. 825-967.
6. Szkodziak P, Krzyżanowski J, Krzyżanowski A, et al. The role of the "beret" sign and other markers in ultrasound diagnostic of the acrania-exencephaly-anencephaly sequence stages. Arch Gynecol Obstet 2020;302:619-28.
7. Langmár Z, Németh M, Csaba Á, Szigeti Z, Joó JG. [Prenatal diagnosis of central nervous system malformations]. Ideggyogy Sz 2013;66:228-34.

8. Levine D, Barnes PD, Robertson RR, Wong G, Mehta TS. Fast MR imaging of fetal central nervous system abnormalities. Radiology 2003;229:51-61.
9. Wald NJ. Prenatal screening for open neural tube effects and Down syndrome: three decades of progress. Prenat Diagn 2010;30:619-21.
10. Hadzagić-Catibusić F, Maksić H, Uzicanin S, et al. Congenital malformations of the central nervous system:clinical approach. Bosn J Basic Med Sci 2008;8:356-60.
11. Domröse CM, Bremer S, Buczek C, et al. Termination of pregnancy following prenatally diagnosed central nervous system malformations. Arch Gynecol Obstet 2018;298:903-10.
12. Hadzagić-Catibusić F, Maksić H, Uzicanin S, et al. Congenital malformations of the central nervous system:clinical approach. Bosn J Basic Med Sci 2008;8:356-60.
13. Ozkan ZS, Gilgin H, Aygün HB, et al. Our clinical experience about prenatal diagnosis and neonatal outcomes of fetal central nervous system anomalies. J Matern Fetal Neonatal Med 2011;24:502-5.
14. Chatzipapas IK, Whitlow BJ, Economides DL. The 'Mickey Mouse' sign and the diagnosis of anencephaly in early pregnancy. Ultrasound Obstet Gynecol 1999;13:196-9.
15. Salamanca A, Gonzalez-Gomez F, Padilla MC, Sabatel RM, Cámara M, Cuadros JL. Prenatal ultrasound semiography of anencephaly: sonographic-pathological correlations. Ultrasound Obstet Gynecol 1992;2:95-100.
16. Coşar E, Köken G, Köken R, et al. Neural Tube Defects and Pregnancy. Turk J Obstet Gynecol 2009;6:193-6.
17. Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. Holoprosencephaly. Orphanet J Rare Dis 2007;2:8.
18. Ohba H, Yamaguchi S, Sadatomo T, Takeda M, Kolakshyapati M, Kurisu K. Surgical resection of large encephalocele: a report of two cases and consideration of resectability based on developmental morphology. Childs Nerv Syst 2017;33:541-5.