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Evaluating 101 cases with the anomaly of fetal central nervous system

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Abstract

Objective: We aimed to determine structural and chromosomal malformations in cases with the anomaly of fetal central nervous system and to evaluate the prognoses of these pregnancies.

Methods: Between 2010 and 2015, 101 cases found to have the anomaly of fetal nervous system were investigated retrospectively. Information such as maternal age, number of gestation, number abortion, week of gestation during diagnosis, anomalies found in ultrasonography, chromosome analysis results and council decision were evaluated.

Results: Cranial anomalies were found only in 26.7% of pregnancies while extracranial anomalies were found in 51.5% of them and abnormal karyotype was found in 11.9% of them. The most common anomaly of central nervous system was ventriculomegaly (51.5%). 68.3% of the pregnancies were terminated by council decision. Extremity anomalies were the most common type of extracranial anomalies (23.8%).

Conclusion: It is necessary to determine concurrent structural and chromosomal anomalies in order to determine prognoses and management of pregnancies with the anomaly of fetal central nervous system.

Keywords: Fetus, chromosomal anomaly, central nervous system, ventriculomegaly.

Özet: Fetal merkezi sinir sistemi anomalili 101 olgunun değerlendirilmesi

Amaç: Fetal merkezi sinir sistemi anomalisi bulunan olgulara eşlik eden yapısal ve kromozomal malformasyonları belirlemek ve bu gebeliklerin prognozlarını değerlendirmektir.

Yöntem: 2010–2015 tarihleri arasında fetal merkezi sinir sistemi anomalisi saptanan 101 olgu retrospektif olarak incelendi. Hastaların anne yaşı, gebelik sayısı, abortus sayısı, tanı aldığı gebelik haftası, ultrasonografide saptanan anomalileri, kromozom analizi sonuçları ve konsey kararları ile ilgili bilgiler değerlendirildi.

Bulgular: Gebeliklerin %26.7'sinde sadece kraniyal anomaliler, %51.5'inde ekstrakraniyal anomaliler ve %11.9'unda anormal karyotip bulunmaktaydı. En sık gözlenen merkezi sinir sistemi anomalisi ventrikülomegali (%51.5) idi. Konsey kararına göre gebeliklerin %68.3'ü sonlandırıldı. Ekstremite anomalileri en fazla görülen ekstrakraniyal anomali tipi idi (%23.8).

Sonuç: Fetal merkezi sinir sistemi anomalisi bulunan gebeliklerin yönetimi ve prognozlarının belirlenmesi için eşlik eden yapısal ve kromozomal anomalilerin belirlenmesi gereklidir.

Anahtar sözcükler: Fetüs, kromozomal anomali, merkezi sinir sistemi, ventrikülomegali.

Introduction

Congenital anomalies affect approximately 2–3% of live births every year.[1] Central nervous system (CNS) anomalies account for about one third of congenital anomalies identified during perinatal period. CNS anomalies are the second most common severe congenital anomalies after cardiac anomalies. Therefore, investigating neurological system is a significant part of routine fetal anomaly screening today. CNS anomalies can be considered as the part of an isolated or systemic syndrome. In addition, structural and chromosomal anomalies may concur in many cases. Also, CNS anomalies are among the common reasons for medical attentions, long-term diseases and deaths. CNS anomalies are the reasons for 75% of fetal deaths and 40% of childhood deaths.[2]

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Identifying any CNS anomaly during prenatal period is very important in terms of determining the possible reason, prognosis and management of the anomaly. Since mortality and morbidity rates are high in fetuses with severe CNS malformation, it is possible to offer the option of terminating pregnancy by informing family if diagnosis is established before viability limit. The aim of this study is to determine structural and chromosomal malformations in cases with the fetal CNS anomaly and to evaluate the prognoses of these pregnancies.

Methods

In this study, we retrospectively evaluated 101 cases found to have fetal CNS anomaly during fetal anomaly screening or routine obstetric ultrasonography (USG) between January 1, 2010 and December 31, 2015 at Gynecology and Obstetrics Clinic of Tepecik Training and Research Hospital. Approval of ethics committee required for the study was obtained from the Local Ethics Committee of Tepecik Training and Research Hospital with the number 29.07.2015/10. All cases were evaluated basically in terms of gestational prognosis and consistency of anomaly with life in the Perinatology Council participated by the specialists from the fields of Perinatology, gynecology and obstetrics, neurosurgery, pediatrics, pathology, genetics, pediatric surgery and radiology.

Information such as maternal age, number of gestation, number abortion, week of gestation during diagnosis, anomalies found in ultrasonography, chromosome analysis results and council decision were obtained from the medical records of patients. Infection parameters of all pregnant women were obtained since ultrasonographic cranial findings associated with intrauterine infections might develop. Patients suspected for intrauterine infection according to the examination results were excluded from the study.

Chorionic villus sampling, amniocentesis or cordocentesis was applied to entire study group for prenatal diagnosis purposes in accordance with the week of gestation. Before the procedure, each family to be done fetal karyotyping was informed in detail about genetic consultancy, methods of karyotyping procedure and complications. Fetal karyotyping procedure was carried out by obtaining informed consent. Chorionic villus sampling was applied to 16 cases at between 10 and 13 weeks of gestation, amniocentesis was applied to 68 cases at between 16 and 22 weeks of gestation, and cordocentesis was applied to 16 cases at between 20 and 28 weeks of gestation by experienced specialists.

The statistical analysis was performed by SPSS 15.0 (SPSS Inc., Chicago, IL, USA). In statistical analysis, categorical variables were presented as number (percentage) and continuous variables were presented as mean ± standard deviation in descriptive findings. In all analyses, statistically significant level was considered as $p<0.05$.

Results

The clinical characteristics of study group are shown in the Table 1. Maternal age was 28.1±6.2, gravida was 2.4±1.4, parity was 1.3±0.8, and abortion was 0.4±0.2. Mean week of gestation that fetal CNS anomaly was identified was 20.6±4.3. Of those, 5.9% were diagnosed at first trimester, 89.1% were at second trimester and 5% at third trimester. Cranial anomalies were found only in 26.7% of pregnancies with CNS anomaly while extracranial anomalies were found in 51.5% of them and abnormal karyotype was found in 11.9% of them. 68.3% of the pregnancies were terminated by council decision.

Structural and chromosomal malformations concurring with fetal CNS anomalies are presented in Table 2. After the evaluation, it was found that fifty-two fetuses had ventriculomegaly, 14 fetuses had anencephaly, 11 fetuses had encephalocele, 6 fetuses had holoprosencephaly, 8 fetuses had corpus callosum agenesis, 1 fetus had schizencephaly, 2 fetuses had intraventricular hemorrhage, 4 fetuses had cerebellar hypoplasia, 4 fetuses had Dandy-Walker malforma-

Table 1. Clinical characteristics of the pregnant women in the study group.*

Maternal age (mean±SD)	28.1	6.2
Gravida (mean±SD)	2.4	1.4
Parity (mean±SD)	1.3	0.8
Abortion (mean±SD)	0.4	0.2
Diagnosis week at pregnancy (mean±SD)	20.6	4.3
First trimester (mean±SD)	6	5.9
Second trimester (mean±SD)	90	89.1
Third trimester (mean±SD)	5	5
Cranial anomaly (n, %)	27	26.7
Extracranial anomaly (n, %)	52	51.5
Abnormal karyotype (n, %)	12	11.9
Gestational termination (n, %)	69	68.3

*The data are presented as mean (mean) ± standard deviation (SD), or n (%).

Table 2. Perinatal outcomes of fetal CNS anomalies.

Anomaly	n	Maternal age (mean±SD)	Week of gestation (mean±SD)	Extracranial anomaly n (%)	Abnormal karyotype n (%)	Gestational termination n (%)
Ventriculomegaly	52	28.3±5.9	21.6±3.5	13 (25)	4 (7.7)	29 (55.8)
Mild	28	29.3±5.4	22.1±3.1	19 (67.9)	3 (10.7)	11 (39.3)
Moderate	8	28.7±6.1	21.7±3.8	5 (62.5)	0 (0)	5 (62.5)
Severe	16	27±4.8	22±2.6	14 (87.5)	1 (6.2)	13 (81.2)
Anencephaly	14	26.2±3.9	16.9±3.7	2 (14.3)	0 (0)	14 (100)
Encephalocele	11	29.1±4.6	17.5±4.6	4 (36.4)	1 (9.1)	11 (100)
Holoprosencephaly	6	29.5±3.7	20.5±4	6 (100)	3 (50)	6 (100)
Corpus callosum agenesis	8	26.6±5.1	24.7±4.5	3 (37.5)	1 (12.5)	6 (75)
Schizencephaly	1	25.8±5.5	23±4.6	1 (100)	0 (0)	1 (100)
Intraventricular hemorrhage	2	28.1±3.8	21.5±4.9	2 (100)	0 (0)	2 (100)
Cerebellar hypoplasia/agenesis	4	29.2±3.5	18.7±1.9	3 (75)	1 (25)	4 (100)
Dandy-Walker malformation	4	28.1±4.3	23.2±3.1	2 (50)	0 (0)	3 (75)
Vermian agenesis	3	29.4±2.9	21±1	1 (33.3)	0 (0)	3 (100)
Blake's pouch cyst	2	32.1±2.4	24.5±9.2	1 (50)	0 (0)	1 (50)
Mega cisterna magna	5	27.4±3.7	22±4.4	3 (60)	0 (0)	3 (60)
Microcephaly	2	29.8±3.1	29±8.5	1 (50)	0 (0)	1 (50)
Arachnoid cyst	3	26.5±4.2	26±9	2 (66.7)	0 (0)	2 (66.7)
Cerebral cyst	2	29.7±3.2	18.5±0.7	1 (50)	0 (0)	1 (50)

CNS: central nervous system, **SD:** standard deviation

tion, 3 fetuses had vermian agenesis, 2 fetuses had Blake's pouch cyst, 5 fetuses had mega cisterna magna, 2 fetuses had microcephaly, 3 fetuses had arachnoid cyst, 2 fetuses had cerebral cyst and 12 fetuses had choroid plexus cyst.

Concurrent extracranial anomalies are shown in Table 3. Extremity anomalies were the most common extracranial anomalies. Chromosomal anomaly was found in 12 cases. Of those, 8 patients had trisomy 18, 2 patients had trisomy 13, 1 patient had trisomy 22 and 1 patient 69XXX syndrome. Concurring cranial and extracranial anomalies in fetuses with chromosomal anomaly are shown in Table 4. While spinal defect was identified only in one case with chromosomal anomaly, multiple fetal anomalies developed in many systems were observed in other 11 cases. It was decided to terminate all these fetuses.

Discussion

Fetal CNS anomalies are severe pathologies seen in 1.4–1.6 of 1000 live births and accompanied with high morbidity.[3] In this study, we evaluated structural and chromosomal malformations in fetuses with CNS anomaly in a single center.

In a study performed between 2009 and 2011, 7485 pregnant women at over 10 weeks of gestation were examined by USG and malformations belonging to CNS were identified in 24 pregnant week. Mean diagnosis week is 23.4. Considering the distribution of diagnosis weeks to trimesters, it is seen that 1 case was

Table 3. Extracranial anomalies accompanying to fetal CNS anomalies.

	n	%
Extremity	24	23.8
Gastrointestinal	18	17.8
Urinary	14	13.9
Cardiac	13	12.9
Skeletal	3	3
Pulmonary	7	6.9
Cystic hygroma	5	4.9
Facial	9	8.9
Genital	1	1
Hydrops	1	1

CNS: central nervous system

Table 4. Clinical characteristics and concurrent anomalies of fetuses with chromosomal anomaly.

Patient no.	Maternal age	Diagnosis week at pregnancy	Cranial anomaly	Extracranial anomaly	Karyotype method	Karyotype
1	43	19	Ventriculomegaly	Extremity and cardiac anomaly	AC	Trisomy 18
2	40	16	Cerebellar hypoplasia	Urinary system and cardiac anomaly	AC	Trisomy 18
3	27	14	Ventriculomegaly	Cystic hygroma, extremity and cardiac anomaly	CVS	Trisomy 18
4	20	23	Corpus callosum agenesis	Extremity and cardiac anomaly	CC	Trisomy 18
5	31	20	Spina bifida	-	AC	Trisomy 18
6	35	21	-	Urinary system, cardiac anomaly, pulmonary dysplasia	AC	Trisomy 18
7	33	19	Ventriculomegaly	Extremity, urinary and gastrointestinal system anomaly	AC	Trisomy 18
8	42	19	-	Extremity, cardiac anomaly, dysmorphic facial appearance	AC	Trisomy 18
9	22	18	Holoprosencephaly	Cleft palate-lip	AC	Trisomy 13
10	30	17	Holoprosencephaly	Cystic hygroma, gastrointestinal anomaly	AC	Trisomy 13
11	37	23	Holoprosencephaly	Gastrointestinal anomaly, micrognathia	AC	Trisomy 22
12	23	12	Encephalocele	Urinary system anomaly	Abortion material	69XXX

AC: amniocentesis, **CC:** cordocentesis, **CVS:** chorion villus sampling

diagnosed at first trimester, 12 cases were diagnosed at second trimester and 11 cases were diagnosed at third trimester. The authors associated the advanced diagnosis week with the low socioeconomic levels of patients and late application dates.[4] In our study, mean week of gestation for diagnosis of fetal CNS anomalies is lower (20.6). Similarly, fetuses diagnosed at third trimester were only 5% of the study group. This finding shows that the diagnosis of fetal CNS anomalies can be established at earlier weeks with technologic developments and wide use of four-dimensional USG. In another study performed on 69 pregnant women between 2007 and 2008, ventriculomegaly was the most common CNS anomaly (44.9%).[5] Onkar et al. found anencephaly as the most common fetal CNS anomaly.[4] However, ventriculomegaly cases were not included in the study as a separate group. Similarly, ventriculomegaly and anencephaly were the most common CNS anomalies in our study.

In previous studies, CNS malformations were determined as the most frequent reason for gestational termination. Wald et al. terminated 40 of 69 pregnancies with fetal CNS malformation.[6] In the same study, anencephaly was the reason in 25% of pregnancies terminated. Similarly, 68.3% of pregnancies with fetal CNS anomaly was decided to be terminated in our study. Termination due to poor fetal prognosis was offered to all pregnant women with fetal anencephaly, encephalocele, holoprosencephaly, schizencephaly, intraventricular hemorrhage and cerebellar hypoplasia. It was found that the rate of termination in pregnancies with fetal ventriculomegaly depends on the severity of ventriculomegaly. Accordingly, 39.2% of fetuses with mild ventriculomegaly, 39.2% of fetuses with moderate ventriculomegaly and 81.2% of fetuses with severe ventriculomegaly were terminated.

Usually, cranial malformation anencephaly is the case which can be detected the earliest sonographically. These anomalies are diagnosed frequently between 10 and 14 weeks of gestation. In the study of Kınay et al. performed to determine fetal anomaly incidence at 11–14 weeks of gestation, anencephaly was the most commonly identified anomaly.[7] There is an anencephaly case in the literature reported at 9 weeks by USG.[8] It is not recommended to establish sonographic diagnosis before 11–12 weeks since normal cranium ossification is observed at 13 weeks although there are cases reported at early weeks.[8,9] While the earliest diagnosis for anencephaly was established at 11 weeks of gestation in our study group, mean diagnosis week is 16.9. The diagnosis week for 32% of our cases was 11–14 weeks. The cases diagnosed at second and third trimesters are frequently the pregnant women at low socioeconomic levels referred to our clinic when they were diagnosed by chance at other centers.

In our study, microcephaly is the CNS anomaly which is diagnosed at the latest during antenatal period. Arachnoid cyst, corpus callosum agenesis and Blake's pouch cyst are the following anomalies, respectively. These anomalies usually do not present any ultrasonic finding during early prenatal period depending on fetal development; however, they appear at late second trimester or third trimester. While termination could be decided for these cases by Perinatology Council when they are diagnosed at earlier weeks, follow-up was decided due to advanced week of gestation.

Many (51.5%) of the cases in our study group had concurrent multiple anomalies. Among the extracranial malformations, the most frequently identified ones were extremity anomalies. A possible reason for this relationship is the increase in the incidence of club foot secondary to neural tube defects. However, it is seen that anomalies may accompany in many other fetal systems. Therefore, fetuses with CNS anomaly should be examined in detail in the USG.

Ventriculomegaly is seen in 5–25/10,000 live births and 5–15% of the cases have aneuploidy. Kalaycı et al. found the abnormal chromosome rate as 4.9% in fetuses with ventriculomegaly.[10] While chromosomal anomaly rate was defined as 1.5–12% in isolated ventriculomegaly, this rate rises up to 9–36% when additional anomalies accompany to ventriculomegaly.[11,12] In our study, we observed chromosomal anomaly in 7.69% of 52 ventriculomegaly cases. We found abnormal karyotype in 10.7% of fetuses with mild ventriculomegaly. These rates show that there is a risk of chromosomal anomaly even slightly in ventriculomegaly, and fetal karyotyping procedure should be recommended to such cases.

Considering other cerebral anomalies, holoprosencephaly is seen in one per 10,000–15,000 births, but this rate is quite higher in fetal abortions (1/250). Chromosomal anomaly risk is very high in holoprosencephaly, and it was found associated with aneuploidy at a rate of 45%. It has particularly risk in terms of trisomy 13, trisomy 18 and triploidy.[13] In our study, we found chromosomal abnormalities in 50% of cases with holoprosencephaly. We found trisomy 13 in two cases and karyotype result of one case was consistent with trisomy 22. Corpus callosum agenesis was observed in 0.3–0.7% of general population and chromosomal anomaly risk is 20%. It is concurrent with trisomy 13, 18, deletions and duplications in particular. In our study, we found trisomy 18 in one of 8 cases (12.5%). Microcephaly is seen in one out of 6250–8500 live births and chromosomal anomaly risk is high.[14] There were two microcephaly cases in our study and karyotype results of both cases were normal. Chromosomal anomaly risk is about 2–3% in anencephaly cases with fatal progress; however, this rate may increase up to 11% in case of additional anomaly.[15] Chromosomal anomaly risk is 7–18% in encephalocele cases which are observed in one out of 3500–5000 live births. While the karyotype results of 14 anencephaly cases observed in our study were normal, we found triploidy in one of 11 encephalocele cases. Dandy-Walker malformation is found in one out of 25,000–30,000 live births and chromosomal anomaly risk is about 35%.[5,6] Güven et al. reported chromosomal anomaly in 3 (37.5%) out of 8 pregnant women found to have Dandy-Walker malformation.[16] In our study, we identified Dandy-Walker malformation in 4 cases and karyotype results of all fetuses were normal. Although incidence of mega cistern magna, cerebellar hypoplasia, intraventricular hemorrhage, vermian agenesis, arachnoid cyst and Blake's pouch cyst is unknown, chromosomal anomaly risk is low in intraventricular hemorrhage, schizencephaly and Blake's pouch cyst and the risk increases in these cases in the presence of additional anomalies.[5,6] In our study, we found trisomy 18 in a cerebellar hypoplasia case with multiple anomalies.

As known, choroid plexus cysts are specifically higher in fetuses with trisomy 18. While the incidence of these cysts is reported as 0.18–3.6% in the normal population, it is 25–70% in those with trisomy 18.[17] Thorpe-Beeston et al. reported that 34 of 83 cases with choroid plexus cyst had other structural anomalies and karyotyping was performed on all of them.[18] They found abnormal karyotype in 20 of 34 fetuses with additional anomaly. On the other hand, karyotype analysis was performed on 12 of 49 fetuses without additional anomaly according to USG and they were all evaluated as normal.[18] In the study of Nadel et al. including 234 pregnant women, the authors reported that 14 cases had structural anomalies which can be detected ultrasonographically, and they found trisomy 18 in the chromosome analysis of 11 cases and triploidy in one case.[19] They examined chromosomal structure of 62 out of remaining 220 fetuses and they found no anomaly in this group which was normal ultrasonographically.[19] In our

study, we found chromosomal anomaly in 6 of 12 fetuses found to have choroid plexus cyst. However, all fetuses with chromosomal anomaly had additional structural anomalies. Therefore, it is necessary to perform a detailed ultrasonography to seek such anomalies in fetuses with choroid plexus cyst. In line with the previous literature, our findings show that the recommendation of fetal karyotyping procedure is necessary in the presence of concurrent anomalies in fetuses with choroid plexus cyst. Karyotyping on cases with isolated choroid plexus is not a routine procedure at our clinic. However, our study shows that fetal karyotyping is performed due to advanced maternal age or increase of risk in screening test although there is no additional anomaly in fetuses with choroid plexus cyst. Therefore, fetal karyotyping is not a recommended procedure if there is no anomaly or other indications accompanying to isolated choroid plexus cases.

Conclusion

Consequently, some anomalies such as microcephaly can appear at late periods of pregnancy although many fetal CNS anomaly can be identified at second trimester screening USG. Therefore, it would be beneficial to re-evaluate cranial anatomy at third trimester USG. On the other hand, concurrent structural and chromosomal anomalies should be determined in order to identify prognoses and management of pregnancies with the anomaly of fetal central nervous system. Thus, detailed USG procedure and karyotype analysis are necessary in pregnancies found to have fetal CNS anomaly. Since CNS anomalies have severe morbidity and mortality, it should be considered to offer gestational termination to families as an option.

Conflicts of Interest: No conflicts declared.

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