Experimental
&
Clinical Article

Evaluation of Associated Structural and Chromosomal Abnormalities in Patients with Fetal Cerebral Ventriculomegaly Detected in Ultrasonographic Imaging

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ABSTRACT

OBJECTIVE: Fetal cerebral ventriculomegaly is defined as enlarged cerebral lateral ventricles. The etiology of fetal cerebral ventriculomegaly is multifactorial. Aneuploidy in ventriculomegaly is detected especially in moderate and severe ventriculomegaly accompanied by structural anomalies. This study aims to evaluate patients with fetal cerebral ventriculomegaly for associated structural and genetic abnormalities and their obstetric and neonatal outcomes.

STUDY DESIGN: This retrospective cohort study was conducted at Dokuz Eylul University Faculty of Medicine, Obstetrics and Gynecology Department between January 2009 and December 2019. Eighty-seven cases were included in the study and were evaluated for associated structural abnormalities. The results of genetic diagnostic tests were evaluated retrospectively. Postpartum information of the cases was obtained from the hospital records and neurodevelopmental development of the newborns was recorded.

RESULTS: Patients were classified as mild, moderate, and severe ventriculomegaly. Concomitant structural abnormalities were observed in 64% of the patients. Corpus callosum agenesis was the most common abnormality. The incidence of accompanying anomalies in severe ventriculomegaly was found to be significantly higher. Invasive prenatal tests were performed on 27 patients and one of them had a chromosomal abnormality. No significant correlation was observed between the incidence of postpartum neurodevelopmental disorders and the degrees of ventriculomegaly.

CONCLUSIONS: Fetal cerebral ventriculomegaly is a dynamic process. The etiology is multifactorial and abnormalities can be detected during follow-up. All patients should be evaluated carefully for associated abnormalities. The cases should also be evaluated for neurodevelopmental outcomes after birth. All diagnosis, follow-up, and treatment options should be handled with a multidisciplinary approach.

Keywords: Associated anomalies, Fetal cerebral ventriculomegaly, Prenatal diagnosis

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Introduction

Fetal cerebral ventriculomegaly is defined as the enlargement of the lateral ventricles on second-trimester ultrasonography. It is diagnosed during the evaluation of the central nervous system (1). It is seen in approximately two out of one thousand births (2).

Ventriculomegaly can be defined as exceeding the threshold value in ultrasonographic measurement of lateral ventricular atrial diameters. From the fifteenth gestational week, this threshold value is accepted as ≥10 mm (+4SD above the mean) (3). Some studies have categorized atrial diameters between 10-15 mm as mild ventriculomegaly and cases that are greater than 15 mm as severe ventriculomegaly (2). In other

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studies, ventriculomegaly was classified as mild (atrial diameter between 10-12 mm), moderate (atrial diameter between 13-15 mm), and severe (atrial diameter >15 mm) (4).

The etiology of fetal cerebral ventriculomegaly is multifactorial. Hydrocephalus, which is a condition that occurs as a result of an increase in the production of cerebrospinal fluid or a decrease in its absorption, is defined as ventriculomegaly in the prenatal period (5). Metabolic disorders of the fetal cerebral tissue, cerebral or cerebellar atrophy caused by hypoxia or infarction may also cause ventricles to seem relatively enlarged (2). Intrauterine infections, especially Cytomegalovirus and Toxoplasma, obstructive disorders such as Dandy-Walker malformation or aqueduct stenosis, developmental abnormalities such as encephalocele, corpus callosum agenesis, chromosomal abnormalities, intracerebral hemorrhages, and migration anomalies can also cause fetal cerebral ventriculomegaly (5,6).

Aneuploidy in ventriculomegaly is detected especially in cases with moderate and severe ventriculomegaly accompanied by structural anomalies (>15%) (7). In isolated ventriculomegaly cases, chromosomal anomalies are observed relatively less frequently.

The prognosis in fetal ventriculomegaly varies depending on the severity of the ventriculomegaly and the presence of associated malformations. Isolated mild-to-moderate ventriculomegaly has the best obstetric and neonatal outcomes (8,9). As ventriculomegaly becomes more severe, the rate of associated abnormalities increases, and the prognosis becomes worse. Additional central nervous system anomalies accompany approximately 60% of severe ventriculomegaly cases. Among these, the most common ones are corpus callosum agenesis and spina bifida.

The most important limitation of ultrasonography in the diagnosis of fetal cerebral ventriculomegaly is the image artifacts caused by the surrounding bone structure and fetal position. These artifacts prevent a complete evaluation of the ventricle and brain parenchyma (10).

Magnetic resonance imaging (MRI) helps evaluate parenchymal damage, migration anomalies, infarcts, germinal matrix hemorrhages, intraventricular hemorrhages, corpus callosum agenesis, and other anomalies accompanying ventriculomegaly (11,12). In the literature, it has been shown that fetal MRI can detect 1.1%-8.9% of anomalies that cannot be visualized by ultrasonography in isolated mild ventriculomegaly (8,13). The major limitations of fetal MRI are the lack of availability, high cost, and poor image quality due to fetal movement (12).

Fetal ventriculomegaly is typically stable in 57% of the patients. Regression occurs in 29% of the patients, and the condition progresses in 14% of the patients (14,15). Obstetric and neonatal outcomes are the worst in patients whose lateral ventricular diameter progresses during follow-up (16). Postnatal abnormalities do not occur in cases where resolution of the ventriculomegaly is observed (17). Hence, it is recommended to perform later scans on regular basis to evaluate the lateral ventricle atrial diameter and associated abnormalities in these cases (18).

In this study, patients with fetal cerebral ventriculomegaly who were admitted to the outpatient clinic and started obstetric follow-up at Dokuz Eylul University Hospital between January 2009 and December 2019 were evaluated for associated structural and genetic abnormalities and obstetric and neonatal outcomes.

Material and Method

This retrospective cohort study was conducted between January 2009 and December 2019 in Dokuz Eylul University Faculty of Medicine, Department of Obstetrics and Gynecology. Between these dates, patients who were found to have ventriculomegaly during their follow-up in our clinic and patients whose diagnosis was confirmed after being referred to us from an external center with a preliminary diagnosis of ventriculomegaly were reached retrospectively. A total of 87 fetal cerebral ventriculomegaly cases were detected. Demographic data and obstetric and perinatal records of patients were obtained from hospital records. All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Dokuz Eylul University (Ethics approval reference number: 6247-GOA, date: 27.10.2021). All procedures were performed according to the Declaration of Helsinki.

Gestational age was established according to the first day of the last menstrual period. Fetal structural anomalies were determined by ultrasonography performed between the 18th and 22nd weeks of pregnancy according to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines (19). Ultrasonographic evaluation of the central nervous system in cases with suspected fetal cerebral ventriculomegaly was performed according to ISUOG guidelines (19).

During the ultrasonographic evaluation, the cases where the atrial diameters of the lateral ventricles were 10 mm or more were defined as ventriculomegaly. Similar to the previous studies, cases with ventriculomegaly were divided into three groups according to the measured values mild ventriculomegaly (10-12 mm), and moderate ventriculomegaly (12-15 mm), and severe ventriculomegaly (>15 mm) (4). Fetal MRI was then performed on all cases with ventriculomegaly for the detection of additional structural anomalies.

The results of fetal MRI and the results of genetic diagnostic tests for the evaluation of possible chromosomal anomalies were evaluated retrospectively.

All cases with fetal cerebral ventriculomegaly detected in our clinic are evaluated in the perinatology council on a case-

by-case basis. The evaluation is done considering the week of gestation, the degree of ventriculomegaly, associated structural and genetic abnormalities, and whether the ventriculomegaly is isolated or complex. Postpartum information of the cases where termination or the continuation of the pregnancy were recommended as a result of the perinatology council was obtained from the hospital records.

Whether surgical treatment was performed after birth; and if so, postoperative complications were recorded.

All cases with cerebral ventriculomegaly detected between the specified period were included in the study. Exclusion criteria were multiple pregnancies, cases whose birth was performed in another center, and whose genetic tests and MRI were performed in another center.

SPSS 24.0 was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, minimum-maximum) were used for the evaluation of the data. Paired groups were compared with the t-test; qualitative data were compared with the chi-square test. $P<0.05$ was accepted as statistically significant.

Results

A total of 87 cases who were found to have fetal cerebral ventriculomegaly within the specified period were included in the study. The mean age was 28.1±5.6 (years) (between 18-43), and the mean gestational week at the time of diagnosis was 24 weeks and 4 days (between 18-34 weeks). The demographic characteristics of the patients are presented in table I.

Patients diagnosed with fetal cerebral ventriculomegaly were classified as mild (10-12 mm), moderate (13-15 mm), and severe (>15 mm) ventriculomegaly. Accordingly, mild ventriculomegaly was detected in 28 of 87 patients (32.2%), moderate in 18 (20.6%), and severe in 41 (47.2%). Mean lateral ventricular atrial diameter was 10.8±0.5 mm in ultrasonography in mild ventriculomegaly, 13.2±0.4 mm in moderate ventriculomegaly, and 19.4±4.9 mm in severe ventriculomegaly (Table II).

Table I: *Demographic characteristics of the patients included in the study*

	n=87 **Mean**±SD, Range	%
Age, years	28±5.6 (18-43)	%100
Parity		
Nulliparous	52	%60
Primiparous	22	%25
Multiparous	13	%15
Gestational week at the time of diagnosis	24+4 (17+6-34)	-
Types of delivery		
Termination	22	%25
Vaginal birth	18	%21
Cesarean section	47	%54
Gestational week at birth		
Termination	22+4 (19-24)	-
Birth	37+3 (28-41)	
Birth weight, grams		
Termination	543.9±168 (350-910)	-
Birth	2858±662 (730-4240)	
Sex		
Male	45	%52
Female	42	%48

Table II: *Distribution of ventriculomegaly in the patient population*

	Number %	**Mean atrial diameter**
Mild Ventriculomegaly (10-12 mm)	28 (%32.2)	10.8±0.5 mm
Moderate Ventriculomegaly (13-15 mm)	18 (%20.6)	13.2±0.4 mm
Severe Ventriculomegaly (>15 mm)	41 (%47.2)	19.4±4.9 mm

Concomitant structural abnormalities were observed on ultrasonography or MRI in 58 (64%) cases. Corpus callosum agenesis-dysgenesis was found to be the most common (22 cases, 25.2%) abnormality accompanying ventriculomegaly. The incidence of accompanying anomalies in severe ventriculomegaly cases was found to be significantly higher than in mild and moderate ventriculomegaly. The distribution of accompanying anomalies is shown in table III.

Prenatal genetic diagnostic tests were performed on 27 patients who accepted the procedure. Chromosomal abnormality was seen in 1 patient (69-XXX), while the remaining 26 patients had a normal karyotype.

Postpartum follow-up information was obtained in 38 (62.2%) of 61 patients whose pregnancy resulted in a birth. Accordingly, 6 babies (15.7%) died within the first year after birth.

Epilepsy was detected in 2 patients who had moderate ventriculomegaly. One of the patients had microcephaly, while the other patient had no associated structural abnormality.

Speech retardation was observed in two cases, of which one had moderate ventriculomegaly and one had severe ventriculomegaly. The associated structural anomaly in the patient with severe ventriculomegaly was hydrocephalus. Another patient with severe ventriculomegaly had speech retardation and gait disorder.

Congenital muscular dystrophy was observed in a patient with severe ventriculomegaly with cerebellar hypoplasia.

In a case with mild ventriculomegaly, the condition progressed after birth. This patient had speech and gait retardation.

Neurodevelopmental disorders were not observed in 11 patients with mild ventriculomegaly, 3 with moderate ventriculomegaly, and 5 patients with severe ventriculomegaly, and their neurological development was reported as normal. No significant correlation was observed between the incidence of postpartum neurodevelopmental disorders and the degrees of ventriculomegaly (Table IV).

Discussion

Fetal cerebral ventriculomegaly is a heterogeneous condition that has a multifactorial etiology and has a wide range of neurodevelopmental consequences. In this study, we analyzed the ventriculomegaly cases in our center and evaluated the chromosomal abnormalities and central nervous system abnormalities that accompany ventriculomegaly.

Table III: *Distribution of accompanying structural anomalies by ventriculomegaly types*

	Mild ventriculomegaly n=28, (%32.1)	**Moderate ventriculomegaly n=18, (%20.6)**	**Severe ventriculomegaly n=41, (%47.1)**	***p***
Associated anomalies	14, (%16)	9, (%10.3)	31, (%35)	
Associated anomalies				
Encephalocele	1	1	-	
Neural tube defect	2	2	-	
CCA-CCD	7	2	13	
Cerebellar hypoplasia	-	-	6	
Cardiac anomalies	-	1	-	
Dandy-Walker	-	1	2	**<0.05**
Intracranial hemorrhage	-	1	3	
Arachnoid cyst	1	-	-	
Lissencephaly	-	-	6	
TORCH	1	1	-	
Micromelia	1	-	-	
Vermian hypoplasia	1	-	-	
Midbrain mass	-	-	1	

Table IV: *Distribution of neurodevelopmental disorders according to ventriculomegaly types*

	Mild ventriculomegaly n=17 (%44.7)		**Moderate ventriculomegaly n=8 (%21)**		**Severe ventriculomegaly n=13 (%34.2)**		***p***
	Yes	No	Yes	No	Yes	No	
Neurodevelopmental disorders	6 (%15.7)	11 (%28.9)	5 (%13.1)	3 (%7.8)	8 (%21)	5 (%13.1)	**NS**

The cases were classified as mild, moderate, and severe ventriculomegaly, and the rates of associated structural abnormalities in each class were compared. Concomitant central nervous system abnormalities were observed in 67% of the patients included in the study. The rate of structural anomalies associated with severe ventriculomegaly cases was found to be significantly higher than in mild and moderate ventriculomegaly cases. This finding is similar to previous studies. Vergani et al. reported that the rate of associated anomalies was 6% in cases where the ventricular atrial diameter was <12 mm, and 56% in cases where it is ≥12 mm (15). In their study, Gaglioti et al. showed the rate of accompanying structural anomalies as 41% in cases where the ventricular atrial diameter is <12 mm, and 76% in cases where it is ≥12 mm (7). In our study, we found a slight increment in the rates of accompanying abnormalities in moderate ventriculomegaly cases compared to mild ventriculomegaly cases, although the difference was not statistically significant.

In our study, the most common structural abnormality accompanying fetal cerebral ventriculomegaly was found to be corpus callosum agenesis, which was observed in 25.2% of the cases. Corpus callosum agenesis was detected in 22 cases, 13 of which were cases with severe ventriculomegaly. In a study in 2005, Gaglioti et al. found associated abnormalities in 60% of severe ventriculomegaly cases and reported that spina bifida and corpus callosum agenesis are the most common structural abnormalities accompanying severe fetal cerebral ventriculomegaly (7). In 2007, Breeze et al. also found that associated anomalies were observed in 65% of fetal cerebral ventriculomegaly cases, and half of them were corpus callosum agenesis (20).

The rate of chromosomal abnormalities in fetal cerebral ventriculomegaly cases has been shown to be 0-14% in many studies (13). Gaglioti et al. reported that aneuploidy is seen in 3-15% of the cases with isolated mild ventriculomegaly cases (5). One of the most recent data on the coexistence of ventriculomegaly and aneuploidy was presented by D'addario and Rossi. These two authors reported the mean incidence of aneuploidy to be 2.7% in isolated mild ventriculomegaly cases in their study (21). However, there are also studies reporting that the incidence of aneuploidy is related to advanced maternal age. In their study, Nicolaides et al. found an inverse relationship between abnormal karyotype and the severity of ventriculomegaly. They also found that aneuploidy is significantly related to advanced maternal age (22). In our study, invasive prenatal tests were applied to 27 patients. Numerical chromosome abnormality was found in 1 (3.7%) of the patients. Conventional chromosomal analysis was performed in the cases and microarray was not performed. In the literature, the relationship between chromosomal abnormalities and ventriculomegaly varies. The reason for the variability of the results may be due to the fact that the mean ages of the patients are different. In this study, the incidence of chromosomal abnormalities was found to be lower than in other studies; since prenatal genetic diagnostic tests, which are also invasive procedures, were not accepted by the majority of the cases and could only be applied in a small number.

In the literature, it has been shown that TORCH is the most common intrauterine infectious etiology related to ventriculomegaly (7). It has been shown that the rate of intrauterine infection in ventriculomegaly is <2% (16,23). In this study, it is not possible to reach a conclusion about the relationship between ventriculomegaly and the infectious etiology due to the small number of patients who have intrauterine infections. However, intrauterine infections were suspected in 2 of the patients; Toxoplasma was detected in one of these patients, and Rubella was detected in the other. No additional structural abnormality was observed except ventriculomegaly in either of the cases, and the diagnosis was made by detecting the agents after PCR examination of the amniotic fluid after positive serology tests.

In previous studies, it has been shown that a lateral ventricular atrial diameter of more than 15 mm at 14-16th gestational week is associated with a poor prognosis (7). In this study, neurodevelopmental results of 38 babies could be reached. Neurodevelopmental disorders were detected in 35% of cases with mild ventriculomegaly, 62.5% of cases with moderate ventriculomegaly, and 62% of cases with severe ventriculomegaly. These rates are higher than other studies in the literature. In a systematic review of 141 patients with ventriculomegaly, Pilu et al. (24) found adverse neurodevelopmental outcomes in 3,8% of cases with atrial diameter <12 mm. However, this rate rises to 14% in cases where the atrial diameter is calculated between 12-15 mm. In a study of 60 patients with mild ventriculomegaly, Signorelli et al. (25) showed normal neurodevelopmental results in all patients. In their study, they considered mild ventriculomegaly as a variant of normal.

One of the limitations of this study is the low number of patients in whom postnatal neurodevelopmental outcomes were evaluated. Also, genetic diagnostic tests only include chromosome analysis and could not be applied to every patient; and this is another limitation of the study.

The strengths of the study are that the diagnosis of ventriculomegaly which was detected on ultrasonography was first confirmed by a gynecologist, and then by a radiologist with fetal MRI. The fact that the patients were classified as mild-moderate-severe ventriculomegaly and that each class was evaluated within itself is one of the strengths of the study.

In conclusion, it should be kept in mind that ventriculomegaly is a dynamic process, and abnormalities that could not be detected before can be detected during obstetric follow-up. Also, it should be kept in mind that the termination of pregnancy in some cases with ventriculomegaly may cause

bias in studies evaluating neurodevelopmental outcomes; the only patients included in those studies are the ones who are followed up until delivery. The cases should also be evaluated in terms of neurodevelopmental outcomes after birth. All diagnosis, follow-up, and treatment options, including expectant management, termination of pregnancy, preterm birth, clinical genetic examination, and diversification of genetic tests and fetal surgery should be handled with a multidisciplinary approach.

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