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General Section

Obstetric and neurodevelopmental outcome in fetal cerebral ventriculomegaly

N.S. Gezer[1], C. Gezer[2], A. Ekin[2], D.C. Yesilirmak[3], U. Solmaz[2], A. Dogan[2], H. Guleryuz[1]

[1] Department of Radiology, Faculty of Medicine, Dokuz Eylul University, Izmir
[2] Department of Perinatology, Izmir Tepecik Training and Research Hospital, Izmir
[3] Department of Neonatology, Faculty of Medicine, Dokuz Eylul University, Izmir (Turkey)

Summary

Purpose: The purpose of this study is to establish the obstetric and early neurological outcomes of fetuses diagnosed with intrauterine ventriculomegaly (VM). *Materials and Methods:* This retrospective study included 27 fetuses with VM diagnosed by ultrasound (US) and referred for in utero magnetic resonance imaging (MRI). US and MRI reports and laboratory test results were obtained including chromosome analysis, congenital infections, and first and second trimester screening tests. Infants were evaluated for clinical outcome for six to 24 months of age. *Results:* Twenty (51%) fetuses had mild and 19 (49%) fetuses had severe VM. Accompanying central nervous system (CNS) anomalies were statistically significantly more common in severe VM group. The outcome of mild VM group was statistically significantly better than in the severe VM group. *Conclusions:* The authors conclude that ventricular dimension is a significant prognostic factor to determine the outcome of fetal cerebral VM. The presence of accompanying CNS anomalies is more common with severe VM and may be considered as an unfavorable indicator for a better outcome.

Key words: Fetal; Outcome; Ventriculomegaly.

Introduction

Ventriculomegaly (VM) is defined as enlargement of the ventricular system due to increased intracranial content of cerebrospinal fluid. Etiology of the abnormality is unknown in the majority of the cases but it may be congenital infections, spina bifida, obstruction of aquaduct flow, Arnold Chiari malformation, Dandy-Walker malformation, chromosomal anomalies or genetic defect.

Fetal VM is the most common sensitive indicator of brain developmental disorders detected by prenatal sonography and reported to occur in 0.3 to 2.5 per 1,000 live births [1]. VM is diagnosed when the atrial width of the lateral ventricles exceed ten mm. It is defined as mild VM when the ventricular width is ten to 15 mm and severe above 15 mm. It can be unilateral when only one ventricle measures ten mm and above. Asymmetric VM is the term used to define that the difference of lateral ventricle width at the atrium is greater than two mm, but both of them are enlarged over ten mm.

The degree of ventricular enlargement and the presence of other central nervous system (CNS) anomalies are two clinical considerations in a fetus with VM [2, 3]. Prenatal ultrasound (US) is the standard modality used to evaluate the CNS, hence it has some limitations even in the most experienced hands. Reverberation artifacts, cranial ossification in the third trimester, oligohydramnios, breech presentation, maternal obesity, and gas are some of the limitations of an optimized visualization. In addition to these limitations, posterior cerebral fossa, myelinisation, cerebral sulcation, and gyration cannot be assessed adequately with US. When the US diagnosis is indefinite or there is a potential for an anomaly that cannot be exactly defined by US, magnetic resonance imaging (MRI) is used as an alternative imaging modality, given the fact that VM has a poor outcome in fetuses with accompanying anomalies [4-11]. Chromosomal anomalies, viral infections, particularly cyto-megalovirus infection, early diagnosis, progressive and bilateral VM, and cerebral parenchymal atrophy are other poor prognostic factors according to literature. The aim of this study is to establish the obstetric and early neurological outcomes of fetuses diagnosed with intrauterine VM.

Materials and Methods

This retrospective study included the fetuses of VM diagnosed using US and referred for in utero MRI to Radiology Department of Dokuz Eylul University Hospital during the period 2007 through 2009. Terminated pregnancies according to perinatology council's decision because of associated CNS anomalies and progressive or severe VM were not included in the study. The study

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was approved by the Independent Bioethics Committee for Scientific Research of the present institutional review board.

Prenatal radiologic imaging

Using a two-dimensional grayscale ultrasonographic system and a 3-7 MHz convex probe, the atrium of the lateral ventricle was measured in the hemisphere distal to the transducer in the axial plane at the level of the thalami. The calipers were positioned inside the echoes generated by the ventricular walls at the smooth caudal termination of the glomus of the choroid plexus according to standard technique [12].

Prenatal MRI was performed on 1.5 Tesla superconducting system unit by using body coil. Fetal brain examination was performed in axial, coronal, and sagittal planes using T2 weighted single shot sequence (time of repetition (TR): 839; time of echo (TE): 80; flip angle: 90 degrees; slice thickness: three mm; matrix: 256; field of view (FOV): 250; rectangular field of view (RFOV): 100; number of acquisition (NEX): one; slice gap: 0). MRIs were reviewed by a 15-year experienced pediatric radiologist. Measurement of the lateral ventricle size at the level of atrium was obtained using electronic calipers and accompanying CNS anomalies were recorded.

Prenatal clinical evaluation

VM was defined as mild when the dimension of the atrium of lateral ventricle was between ten to 15 mm and severe when it was above 15 mm. Laboratory test results were obtained including chromosome analysis, congenital infections, and first and second trimester screening tests.

Postnatal follow-up

Physical and neurological examinations of the infants were performed by the same consultant neonatologist for six to 24 months of age using Denver Developmental Screening Test, audiometric test, weight, height, and head circumference measurements. Postnatal clinical examinations included mental status, strength, deep tendon reflexes, posture, and tone. Transfontanel US, brain computed tomography or brain MRI was performed if necessary. Neurophysiologic evaluation of infants who could not be followed up in this protocol was performed by a parental questionnaire via phone calls and by collected patient files. They were recalled to the hospital for additional investigation if necessary.

Cases were classified as good outcome and poor outcome groups. Infants with normal neurodevelopment were classified as good outcome group. The ones that died in the antenatal period and with mild or severe neurodevelopmental delay were classified as poor outcome group.

Statistical analysis

Collected data was assessed by using Pearson Chi-Square test and Fisher's Exact test. A p value < 0.05 was considered to indicate statistical significance. All statistical tests were performed using the SPSS software, version 20.0.

Results

A total of 27 fetuses were included in the study. Fourteen (52%) had mild and 13 (48%) had severe VM at the time of the initial diagnosis. Mean lateral ventricular atrial diameter was 13.1 mm and 21.1 mm in mild and severe VM groups, respectively. Asymmetric VM was detected in four cases. Four cases were found to have unilateral VM.

In five of 13 severe VM cases, other fetal CNS anomalies were identified at prenatal MRI examination, including two germinal matrix hemorrhages, a cerebellar hypoplasia, an agenesis of corpus callosum, and a delayed cerebral sulcal development. Two of the 14 mild VM cases had accompanying CNS anomalies which were a delayed cerebral sulcal development with cerebellar hypoplasia and an agenesis of corpus callosum. Accompanying CNS anomalies were statistically significantly more common in severe VM group ($p < 0.005$).

Immunoglobulin (Ig) G and Ig M antibodies against toxoplasma, rubella, cytomegalovirus and herpes virus (TORCH) were assayed in maternal serum in all cases and there were no evidence of intrauterine infection. One case with mild VM had high risk at first trimester screening test. Two cases of severe VM included one case of mild VM that was high-risk at second trimester screening test. None of them had any chromosomal abnormalities.

Three cases died in utero. Two of the 24 live born infants died in the early neonatal period. Surviving infants were followed up between six to 24 months. Four cases had severe neurodevelopmental delay. Two cases were diagnosed as having a mild neurodevelopmental delay at follow up. Sixteen cases had normal neurodevelopment. Table 1 summarises prenatal fetal MRI findings and prognosis of the fetuses.

Sixteen cases (59%) with normal neurodevelopment were classified as good outcome group, while a total of 11 cases (41%) which died in the antenatal or postnatal period with mild or severe neurodevelopmental delay were classified as poor outcome group.

The mild VM group had a better outcome than the severe VM group and the outcome of mild VM group was statistically significantly better ($p < 0.005$). Table 2 shows the outcome of mild and severe VM groups.

Discussion

In the present study, cases with mild VM had a better outcome than the severe VM group and the outcome of mild VM group was statistically significantly better in accordance with the literature. Previous reports have revealed that lateral ventricular atrial width is strongly related with the outcome of VM [1, 13, 14]. Kirkinen *et al*. followed up 25 fetuses with VM at 10.1 (standard deviation ± 2.6) years of age and found that the fetuses with severe handicaps on long-term follow up had more severe ventricular dilatation than the fetuses with good long-term outcomes [15]. Breeze *et al*. in their research studied obstetric and neonatal outcomes in 20 severe VM cases. Nine out of ten live born babies had abnormal outcomes [16]. However, in an isolated mild VM outcome research, Gomez-Arriage *et al*. and Kutuk *et al*. found that 72.2% and 64% of infants showed completely normal postnatal outcomes, respectively [17, 18]. Sixty- four

Table 1. — *Prenatal fetal MRI findings and prognosis of the fetuses.*

Case no.	Ventriculomegaly	Asymmetric/ unilateral	Accompanying or unilateral ventriculomegaly	Prognosis of central nervous system anomalies
1	Mild	-	-	Severe neurodevelopmental delay
2	Mild	-	-	Normal neurodevelopment
3	Mild	-	-	Normal neurodevelopment
4	Mild	-	Delayed cerebral sulcal development and cerebellar hypoplasia	Died in utero at 30 weeks
5	Mild	-	-	Normal neurodevelopment
6	Severe	-	Germinal matrix hemorrhage	Normal neurodevelopment
7	Severe	-	Germinal matrix hemorrhage	Severe neurodevelopmental delay
8	Mild	Unilateral	-	Normal neurodevelopment
9	Severe	-	-	Severe neurodevelopmental delay
10	Severe	-	Cerebellar hypoplasia	Died in utero at 38 weeks
11	Severe	-	-	Died after postpartum three hours
12	Severe	-	-	Normal neurodevelopment
13	Severe	-	Agenesis of corpus callosum	Mild neurodevelopmental delay
14	Severe	Asymmetric	-	Died after postpartum two hours
15	Mild	-	-	Normal neurodevelopment
16	Mild	Unilateral	-	Normal neurodevelopment
17	Severe	Asymmetric	-	Severe neurodevelopmental delay
18	Mild	-	-	Normal neurodevelopment
19	Mild	-	-	Normal neurodevelopment
20	Mild	-	Agenesis of corpus callosum	Normal neurodevelopment
21	Mild	-	-	Normal neurodevelopment
22	Severe	-	-	Normal neurodevelopment
23	Severe	Asymmetric	Delayed cerebral sulcal development	Mild neurodevelopmental delay
24	Mild	Unilateral	-	Normal neurodevelopment
25	Severe	Asymmetric	-	Normal neurodevelopment
26	Severe	Unilateral	-	Normal neurodevelopment
27	Severe	-	-	Died in utero at 21 weeks

Table 2. — *Outcomes of mild and severe VM groups (n, %).*

	Good outcome	Poor outcome	Total
Mild ventriculomegaly	12 (85.7%)	2 (14.3%)	14 (100%)
Severe ventriculomegaly	4 (30.8%)	9 (69.2%)	13 (100%)
Total	16 (59.3%)	11 (40.7%)	27 (100%)

$p = 0.004$.

cases of VM from birth up to four years were followed up in another study which revealed that the degree of antenatal VM was related to pediatric neurological morbidity, and when lateral ventricular atrial diameter was over 15 mm, it was associated with an increase in abnormal neurological development [13].

Accompanying fetal anomalies are one of the poor prognostic factors in VM [10, 19-21]. It is reported that associated structural anomalies significantly worsen the outcome, and fetal and neonatal deaths are much more frequent in this group [22]. In the present study, five (71%) of seven live born fetuses with accompanying CNS anomalies had poor outcome. On the other hand, only six of 20 fetuses (30%) in the isolated VM group had poor outcome. Although the outcome of fetuses with accompanying CNS anomalies was twice as worse than the isolated VM group, and this finding correlates well with the previous reports, we must consider that VM was severe in four of the five fetuses with poor prognosis in the associated anomaly group. Thus it can be speculated that the poor prognosis of the fetuses with accompanying anomalies could also be associated with the severity of VM rather than with the accompanying anomalies itself. To establish the consequence of accompanying CNS anomalies, it must be mentioned that case no. 4, which had mild VM but delayed cerebral sulcal development and cerebellar hypoplasia, died in utero at 30 gestational weeks. On the contrary, cases no. 25 and 26 with isolated severe VM had normal neurodevelopment. However it also must considered that these two cases were followed up to six months which may be a short period of time to determine an exact outcome. Case no. 1 was the unique and mysterious case of this study with isolated mild VM, which had severe neurodevelopmental delay. The authors assume that more detailed investigations are required to disclose this case.

The correlation between accompanying CNS anomalies and the degree of VM has also been studied by researchers. In a study of fetuses with VM, the pregnancy

outcome and neurodevelopmental outcome at an age of more than 24 months were evaluated [23]. It was suggested that cases with ventricular width above 12 mm were more often associated with malformations and had a normal neurodevelopmental outcome less frequently [23]. Griffiths *et al*. in their prospective study of fetuses with isolated VM found that severe VM was associated with an approximate ten-fold increase in the risk of another brain abnormality being present when compared with fetuses with mild VM [24]. Broomley *et al*. followed 36 live born infants with VM and revealed that fetuses with mild VM had a lower incidence of accompanying anomalies and a better outcome than fetuses with more severe ventricular dilatation [10]. In the present study, five out of 13 severe VM cases had accompanying CNS anomalies and accompanying CNS anomalies were statistically significantly more common in severe VM group in accordance with the literature.

In previous studies, asymmetric lateral ventricles and bilateral enlargement are approved to be one of the poor prognostic factors in VM. Ouahba *et al*. in their outcome research of isolated mild VM found that asymmetrical bilateral enlargement of ventricles was associated with poor outcome [25]. In the present study, only one (case no. 25) of four (20%) live born infants with asymmetric VM had a good outcome. Although the results were remarkable, they were not significant because a larger number of cases is needed for statistical significance. All four unilateral VM cases had good outcome, including case no. 26 which had severe unilateral ventricular dilatation. The present result is in accordance with the previous research by Leitner *et al*. who studied outcome of isolated mild VM and found that outcome of unilateral VM is generally positive on both the neurodevelopment and cognitive tests [26].

The present authors acknowledge three limitations in this study. Firstly, the small number of the study group may limit the strength of the results. Secondly, the follow-up period ranged between six and 24 months, which is a short period of time to assess an exact outcome for fetal VM. Finally, the present follow-up protocol was heterogeneous because of social conditions in this country.

Conclusion

Recently many researches have been performed to study the outcome of fetal cerebral VM. Risk and degree of neurodevelopmental delay are still not definitive but also not unclear. Considering the literature and the results of the present study, the authors conclude that ventricular dimension is a significant prognostic factor to determine the outcome of fetal cerebral VM. The presence of accompanying CNS anomalies is more common with severe VM and may be considered as an unfavorable indicator for a better outcome.

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Address reprint requests to:
N. S. GEZER, M.D.
Department of Radiology,
Dokuz Eylul University School of Medicine,
Mithatpasa Str., 35340 Inciralti, Izmir (Turkey)
e-mail: drsinemgezer@gmail.com