The prognostic role of prenatal MRI volumetric assessment in fetuses with isolated ventriculomegaly

Naciye Sinem Gezer[1], Handan Güleryüz[1], Cenk Gezer[2], Ali Koçyiğit[3], Didem Yeşilırmak[4], Atalay Ekin[2], Muzaffer Bilgin[5], İbrahim Egemen Ertaş[2]

[1]Department of Radiology and [4]Division of Neonatology, Department of Pediatrics, Dokuz Eylul University Faculty of Medicine, [2]Department of Perinatology, Tepecik Training and Research Hospital, Izmir, [3]Department of Radiology, Pamukkale University Faculty of Medicine, Denizli, and [5]Department of Biostatistics and Medical Informatics, Osmangazi University Faculty of Medicine, Eskisehir, Turkey. E-mail: drsinemgezer@gmail.com

Received: 31 October 2014, Revised: 7 January 2015, Accepted: 26 January 2015

SUMMARY: Gezer NS, Güleryüz H, Gezer C, Koçyiğit A, Yeşilırmak D, Ekin A, Bilgin M, Ertaş İE. The prognostic role of prenatal MRI volumetric assessment in fetuses with isolated ventriculomegaly. Turk J Pediatr 2015; 57: 266-271.

In this prospective study, we aimed to establish the value of volumetric assessment by prenatal brain MRI in determining the prognosis of fetuses with isolated VM.

A total of 23 fetuses with isolated VM were included in the study. Supratentorial cerebral parenchyma volume (PV) and ventricular volume (VV) were measured, and supratentorial ventricular/parenchymal volume (VV/PV) ratios were calculated. Pregnancy and postnatal neurodevelopmental outcomes up to two years of age were obtained and correlated with the volumetric measurements.

VV was found to be strongly and positively correlated with ventricular dimension. There was a statistically significant difference between the VV/PV ratios of the good and poor prognosis groups into which the cases had been categorized. The fetuses with a poor prognosis had a significantly higher VV/PV ratio.

Volumetric parenchymal and ventricular measurements obtained by fetal brain MRI may contribute to future clinical studies concerning the evaluation of fetuses with VM and provide an important indicator in cases where management dilemmas arise.

Key words: fetus, magnetic resonance imaging, prognosis, ventriculomegaly, volume.

Cerebral ventriculomegaly (VM) is the most common central nervous system anomaly detected during prenatal sonography and the most common indication for prenatal magnetic resonance imaging (MRI)[1-3]. The dimension of the lateral ventricles is normally quite stable throughout pregnancy, at around 7.6 ± 0.6 mm. The ventricles are considered to be dilated when the atrial diameter is 10 mm or greater at any gestational age, and ventriculomegaly is said to be severe when the atrial diameter exceeds 15 mm[2]. The atrial diameter/diameter of the cerebral parenchyma ratio has also been discussed in the literature and seems to be constant at approximately 0.35[4].

Management of VM is complicated because of the wide number and variety of reported outcomes. Considering the physical difficulties faced by disabled children, and the ethical issues that such cases present for families and the community, it is crucial to be able to predict outcomes. According to previous studies, neurological outcome seems to be worse when the VM is severe, progressive and asymmetric. Fetuses with associated brain anomalies, cortical thinning, chromosome anomalies and intrauterine infections may have a poor prognosis[5-9].

Although ultrasonography is the basic modality to scan fetal anomalies and follow central nervous system (CNS) development, volumetric assessments by fetal MRI may provide additional information and help in establishing the prognosis of these fetuses more accurately.

According to previous studies, supratentorial parenchyma and lateral ventricular volumes can be measured reliably on fetal MRI, and the image plane is not an important factor for assessment[10]. We speculate that since the brain and ventricles are three-dimensional structures, two-dimensional measurement may not reveal their status correctly.

In this prospective study, we aimed to establish the value of volumetric assessment by prenatal brain MRI in determining the prognosis of fetuses with mild and severe isolated VM.

Material and Methods

This prospective study was conducted after receiving approval from the Noninterventional Research Ethics Board at our institution. Written informed consent was obtained for each case. Cases of fetal VM referred to our hospital between December 2007 and September 2009 for fetal brain MRI due to the presence of a suspected CNS anomaly on prenatal ultrasound were included in the study.

Magnetic resonance imaging was performed on a 1.5-T unit (Integra, Philips, the Netherlands) using a body coil, on the same day or the day after diagnosis of fetal VM was made by ultrasonography. Neither maternal sedation nor IV contrast material was used. Axial, coronal and sagittal plane images were obtained using a T2 weighted single-shot (SS) sequence (TR: 839; TE: 80; flip angle: 90 degrees; slice thickness: 3 mm; matrix: 256; FOV: 250; RFOV: 100; NSA:1; Slice gap: 0). The images were prospectively reviewed by a pediatric radiologist with 15 years of experience. Fetuses with associated anomalies were excluded from the study. Ventricle diameter assessment was performed at the level of the glomus of the choroid plexus on a transverse slice. The calipers were positioned inside the echoes generated by the ventricular walls. Ventriculomegaly was considered mild when the atrial diameter was 10-15 mm, and severe when it exceeded 15 mm, in accordance with previous studies[11].

Two-dimensional images were transferred to Workstation (View Forum Workstation R5.1 Philips Healthcare, the Netherlands) for post-processing. The sequence and image plane having the least motion and including the entire brain was assessed by the radiologist for volumetric calculations and reconstructed with slices 1 mm in thickness. Segmentation was performed manually, slice by slice, employing hand tracing of a free-form region of interest (ROI) on each image of the selected sequence and image plane (Fig. 1). Supratentorial ventricular volume (VV) (including the choroid plexus) and supratentorial cerebral volume were calculated separately (Figs. 2, 3 and 4). Supratentorial parenchymal volume (PV) was obtained by subtracting ventricular volume from cerebral volume. The supratentorial ventricular/parenchymal volume (VV/PV) ratio was calculated using the formula supratentorial ventricular volume/parenchymal volume x 100.

After birth, neurophysiologic examinations of the cases were performed by the same

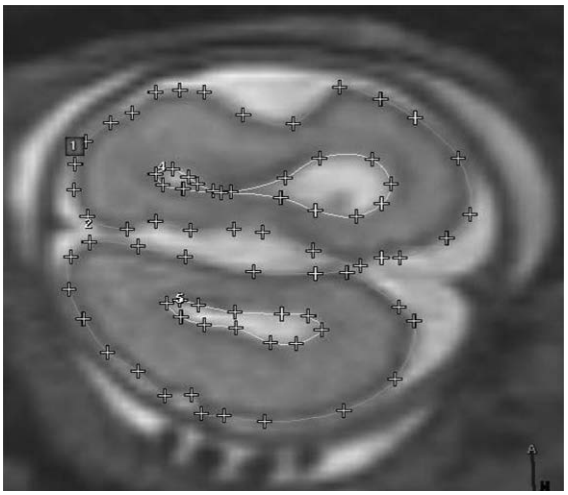

Fig. 1. MRI image showing manual segmentation of cerebral hemispheres and ventricles of a 25-week-old fetus.

Fig. 2. Three-dimensional image of supratentorial ventricles from superior at 32 weeks' gestation.

neonatologist. The assessment included the Denver Developmental Screening Test, an audiometric test, and weight, length and head circumference measurements. Transfontanel ultrasonography, cranial computed tomography and cranial MRI were performed if necessary. Additional data on neurophysiologic development were collected via hospital records and by telephone, using a questionnaire (Table I) modified from that used by Ouahba et al.[12].

The cases included in the study were classified into two groups: "good prognosis" and "poor prognosis." Infants with normal physical and neurologic development and no health issues associated with VM were included in the "good prognosis" group, while those who died in the antenatal or postnatal period due to VM; underwent cesarean section upon the decision of our hospital's perinatology council on the basis of known poor prognostic factors such as progressive VM, intrauterine growth retardation, chromosome anomalies and intrauterine infections; and infants with neurodevelopmental delay or growth retardation were included in the "poor prognosis" group. Pregnancy and postnatal neurodevelopmental outcomes up to two years of age were obtained and correlated with the volumetric measurements.

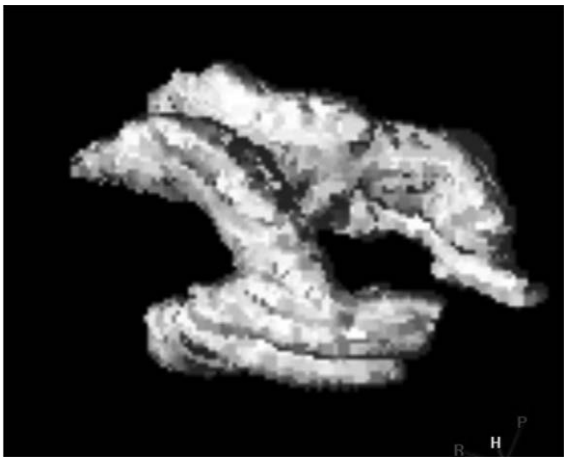

Fig. 3. Three-dimensional images of supratentorial ventricles from posterolateral at 32 weeks' gestation.

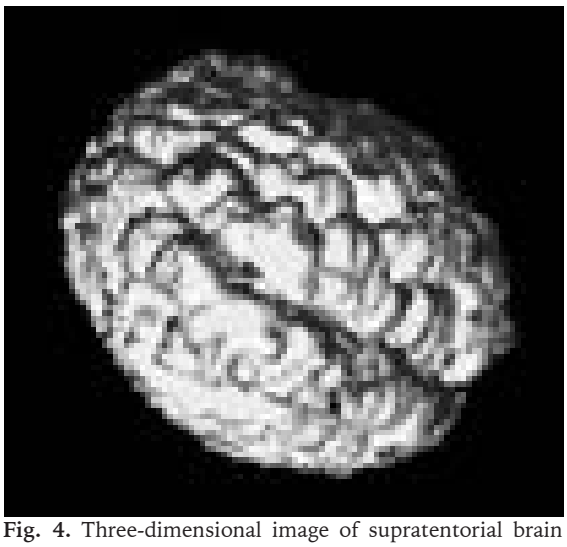
Fig. 4. Three-dimensional image of supratentorial brain parenchyma from superior at 32 weeks' gestation.

Statistical Analysis

Continuous variables are expressed as mean ± SD, categorical variables are given as a percentage. The normality of the variables was analyzed using the Shapiro–Wilk test. The normally distributed variables were compared using the nonparametric Mann–Whitney U test. To determine the direction and magnitude of the correlation between variables which fit in a normal distribution, Spearman correlation coefficients were calculated. Categorical variables were analyzed using Fisher's exact test. A *p*-value less than 0.05 was considered statistically significant. All statistical tests were performed using IBM SPSS for Windows, Version 21.0 (Armonk, NY: IBM Corp.).

Results

Thirty-nine cases were referred to our hospital for fetal brain MRI between December 2007 and September 2009. Sixteen of the 39 cases were excluded from the study, since the prognosis of VM would be affected by accompanying CNS anomalies. None of the 23 patients in the study group had chromosomal anomalies or suffered from intrauterine infections that would influence the prognosis. The mean gestational age of the study group was 24 weeks, ranging from 17 to 34 weeks of gestation. Fifteen cases had mild VM, while in 8 cases VM was severe.

In 4 cases, termination of pregnancy was performed upon the decision of the perinatology council due to progression of VM or intrauterine growth retardation. One case died unexpectedly in utero. One of the 18 live births survived less than three hours after birth. Surviving infants were followed up to 24 months. Two cases had progressive hydrocephalus, and a ventriculoperitoneal (VP) shunt was inserted. One of these cases died due to VP shunt

Table I. Questionnaire

Case no.:
Date of birth:
Does your child have a health problem?
Has your child previously been hospitalized? If yes, for what reason?
At which age did your child first: Smile Grasp objects Sit Walk Say his/her first words
Has your child previously undergone any radiologic imaging, e.g., transfontanel ultrasonography, cerebral computed tomography, cerebral magnetic resonance imaging?
Has your child previously undergone any tests, e.g., the "Denver test," or an audiometric test?

infection. Three cases, including the one just mentioned, had severe neurodevelopmental delay. Thus, a total of 9 cases had a poor prognosis. The remaining 14 cases, with a good prognosis, were healthy and displayed normal neurodevelopment.

The mean supratentorial PVs of the good prognosis and poor prognosis groups were 103.9 (SD ± 61.8) and 64.4 (SD ± 35.1) respectively. The median VVs and VV/PV ratios of the good prognosis group were 15.4 (12.2-21.3) and 16.7 (12.5-22.8) respectively. The median VVs and VV/PV ratios of the poor prognosis group were 19.7 (10.9-69.5) and 47.0 (18.1-138.7) respectively. No significant difference was found between the VVs or the PVs of the good and poor prognosis groups ($U=48.00$, $p=0.368$; $t=1.736$, $p=0.097$). However, there was detected a statistically significant difference between the VV/PV ratios of the good and poor prognosis groups ($U=27.50$, $p=0.023$).

Statistically significant differences between the VVs and VV/PV ratios of the mild and severe VM groups ($U=10.00$, $p=0.001$) were found. However, there was no statistically significant difference between the PVs of these groups ($t=0.649$, $p=0.532$; $U=32.00$, $p=0.076$). In addition, supratentorial VV was found to be strongly and positively correlated with ventricular dimension ($r=0.766$, $p<0.001$). However, ventricular dimension was not correlated with PV or V/P ratio ($r=0.277$, $p=0.0201$; $r=0.381$, $p=0.073$). Table II shows the gestational age, ventricular dimension, VV, PV, VV/PV ratio and prognosis of each case.

Discussion

Volumetric assessment of the fetal brain and ventricles has been studied by some researchers in recent years. Grossman et al.[13] investigated the quantitative MRI measurements of human fetal brain development in utero, and discovered that the volume of the lateral ventricles does not change significantly between the gestational weeks of 25 and 41. They also found a statistically significant difference between the supratentorial VV of 27 normal fetuses and that of 6 fetuses with VM[13]. It has been shown that supratentorial VV is significantly and positively correlated with ventricle dimension and that the volume of the lateral ventricles is significantly higher in VM[10,13]. Confirming previous studies, we revealed a statistically significant difference between the VV of mild and severe VM groups, and found ventricle dimension to be strongly and positively correlated with VV.

Grossman et al.[13] also found that cerebral parenchyma volume is strongly and positively correlated with gestational age in normal fetuses. However, they did not detect a significant difference in the PV of a VM group when compared to that of normal fetuses. Kazan-Tannus et al.[10] reported that PV was higher in a normal study group than in fetuses with VM, but they did not find a significant difference between the PVs of mild and severe VM groups. In accordance with their findings, no statistically significant difference was detected between the PVs of mild and severe isolated VM groups in this study, which also did not find PV to be correlated with ventricle dimension. Looking at the results of previous studies as well as our own findings,

Table II. Ventricular Dimension, Supratentorial Parenchymal Volume, Ventricular Volume, Ventricular/Parenchymal Volume Ratio and Prognosis of the Cases in the Follow-Up Period

Case no.	Gestational age	Ventricular dimension	PV	VV	VV/PV	Prognosis
1	22	11.4	55.2	10.5	19	Severe neurodevelopmental delay
2	21	15.8	32.5	21.3	65.5	Progressive VM – termination of pregnancy at 22 weeks
3	22	12.2	57.4	14.5	25.3	Normal neurodevelopment
4	32	12.6	199.3	19.2	9.6	Normal neurodevelopment
5	25	14.8	115.2	19.7	17.1	Progressive VM – termination of pregnancy at 28 weeks
6	20	11.0	37.4	7.8	20.8	Normal neurodevelopment
7	30	12.3	165.8	12.7	07.7	Normal neurodevelopment
8	17	18.0	71.0	33.4	47.0	Severe neurodevelopmental delay – died at 8 months due to VP shunt infection
9	34	16.2	213.3	27.8	13.0	Normal neurodevelopment
10	27	28.7	118.4	105.6	81.9	Died at 2 hours postpartum
11	26	12.2	115.8	20.3	17.5	Normal neurodevelopment
12	23	14.0	58.2	12.6	21.6	Normal neurodevelopment
13	22	12.3	51.8	11.3	21.8	Progressive VM – termination of pregnancy at 23 weeks
14	21	13.0	56.5	8.9	15.8	Progressive VM – termination of pregnancy at 32 weeks
15	20	41.0	69.4	135.7	195.5	Severe neurodevelopmental delay – VP shunt was inserted
16	20	12.1	29.7	10.8	36.4	Normal neurodevelopment
17	18	12.8	23.4	24.3	103.8	Normal neurodevelopment
18	25	11.0	68.2	9.0	13.2	Normal neurodevelopment
19	29	12.0	111.4	17.6	15.8	Normal neurodevelopment
20	26	10.7	97.9	13.8	14.1	Normal neurodevelopment
21	25	19.8	129.8	28.5	22.0	Normal neurodevelopment
22	29	15.2	146.8	16.2	11.0	Normal neurodevelopment
23	19	14.4	9.9	19	201.0	Died in utero at 21 weeks

PV: supratentorial cerebral parenchyma volume; VV: supratentorial ventricular volume; VV/PV: supratentorial ventricular/parenchymal volume ratio; VP: ventriculoperitoneal

we conclude that PV is not directly related to ventricular size and dilatation, presumably due to the open cranial sutures of the fetus which allow for preservation of the parenchyma by increasing the head circumference.

Various studies have been conducted to determine the prognosis of VM, but only a few of them have investigated the effect of supratentorial VV and PV on postnatal outcomes in fetuses with VM. Recently, Pier et al.[14] reported a study on magnetic resonance volumetric assessment of the brain in fetuses

with ventriculomegaly, but their results are not in accordance with ours. They suggested that high VV correlates with poor postnatal outcome in fetuses with VM, regardless of whether the latter is isolated or exists in association with other CNS anomalies, but found that PV was not associated with either normal or abnormal outcome. However, in contrast to their findings, neither VV nor PV differed significantly between the good and poor prognosis groups in this study. Only in the VV/PV ratio was a significant difference found between the two groups. Supporting our findings, the above-mentioned study by Grossman et al.[13] demonstrated that fetuses with growth retardation or brain parenchyma loss had a significantly higher supratentorial VV/PV ratio. We speculate that increased VV/PV ratio could be an indirect indicator of elevated intracranial pressure, which would give rise to a poor prognosis due to restricted blood flow into the brain. Although it is said that poor prognosis is associated with severe VM and cortical thinning, these two variables may be dependent or independent from each other. Furthermore, VM may be asymmetric or unilateral. Thus, evaluation of these prognostic factors separately, on the basis of two-dimensional measurements, may not provide adequate, detailed information concerning the prognosis of VM. Volumetric measurements and VV/PV ratio calculation may contribute to a better evaluation of these three-dimensional intracranial structures.

Our study had some limitations. One of these was the twenty-four-month follow-up period, which is relatively short. Extending follow-up as far as the early school years would help to evaluate outcome more accurately. The variation in gestational weeks was also a limitation; however, the VV/PV ratio was calculated in order to eliminate this issue. The small number of fetuses was another limitation.

In conclusion, our preliminary data indicated that poor prognosis of isolated fetal VM may be associated with a higher VV/PV ratio. Volumetric measurements of the supratentorial brain parenchyma and ventricles obtained by fetal brain MRI may be helpful in the evaluation of fetuses with VM and provide an important indicator in cases where management dilemmas arise. Long-term studies on large groups are required to more clearly demonstrate the possible prognostic utility of volumetric MRI assessment in fetuses with VM.

REFERENCES

1. Kelly EN, Allen VM, Seaward G, Windrim R, Ryan G. Mild ventriculomegaly in the fetus, natural history, associated findings and outcome of isolated mild ventriculomegaly: a literature review. Prenat Diagn 2001; 21: 697-700.
2. Salomon LJ, Ouahba J, Delezoide AL, et al. Third-trimester fetal MRI in isolated 10- to 12-mm ventriculomegaly: is it worth it? BJOG 2006; 113: 942-947.
3. Siegelman ES. Body MRI. Philadelphia, PA: Elsevier Saunders 2005; 343-369.
4. Hilpert PL, Hall BE, Kurtz AB. The atria of the fetal lateral ventricles: a sonographic study of normal atrial size and choroid plexus volume. AJR Am J Roentgenol 1995; 164: 731-734.
5. Durfee SM, Kim FM, Benson CB. Postnatal outcome of fetuses with the prenatal diagnosis of asymmetric hydrocephalus. J Ultrasound Med 2001; 20: 263-268.
6. Gupta JK, Bryce FC, Lilford RJ. Management of apparently isolated fetal ventriculomegaly. Obstet Gynecol Surv 1994; 49: 716-721.
7. Lipitz S, Yagel S, Malinger G, Meizner I, Zalel Y, Achiron R. Outcome of fetuses with isolated borderline unilateral ventriculomegaly diagnosed at mid-gestation. Ultrasound Obstet Gynecol 1998; 12: 23-26.
8. Senat MV, Bernard JP, Schwärzler P, Britten J, Ville Y. Prenatal diagnosis and follow-up of 14 cases of unilateral ventriculomegaly. Ultrasound Obstet Gynecol 1999; 14: 327-332.
9. Kinzler WL, Smulian JC, McLean DA, Guzman ER, Vintzileos AM. Outcome of prenatally diagnosed mild unilateral cerebral ventriculomegaly. J Ultrasound Med 2001; 20: 257-262.
10. Kazan-Tannus JF, Dialani V, Kataoka ML, et al. MR volumetry of brain and CSF in fetuses referred for ventriculomegaly. AJR Am J Roentgenol 2007; 189: 145-151.
11. Leitner Y, Stolar O, Rotstein M, et al. The neurocognitive outcome of mild isolated fetal ventriculomegaly verified by prenatal magnetic resonance imaging. Am J Obstet Gynecol 2009; 201: 215.e1-e6.
12. Ouahba J, Luton D, Vuillard E, et al. Prenatal isolated mild ventriculomegaly: outcome in 167 cases. BJOG 2006; 113: 1072-1079.
13. Grossman R, Hoffman C, Mardor Y, Biegon A. Quantitative MRI measurements of human fetal brain development in utero. Neuroimage 2006; 33: 463-470.
14. Pier DB, Levine D, Kataoka ML, et al. Magnetic resonance volumetric assessments of brains in fetuses with ventriculomegaly correlated to outcomes. J Ultrasound Med 2011; 30: 595-603.