

Morphological evaluation of lateral ventricles of fetuses with ventriculomegaly by three-dimensional ultrasonography and magnetic resonance imaging: correlation with etiology

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Abstract

Purpose To evaluate morphology of lateral ventricles of ventriculomegaly/hydrocephaly fetuses using 3D-sonography by virtual organ computer-aided analysis (VOCAL) technique and magnetic resonance imaging (MRI) and verify morphologic patterns related to etiology.

Methods Seventeen fetuses presenting with ventricular enlargement (atria > 10 mm) were evaluated. 3D datasets were acquired from a coronal reference plane and post-processed by the rotational imaging using VOCAL 30°. MRI study was analyzed in the three plans in all sequences. Morphologic aspects such as global shape, anterior, posterior and inferior horn characteristics, wall irregularities and deformities were analyzed and related to etiology factor.

Results Twenty-nine percent of the cases were secondary to Arnold–Chiari syndrome and presented with global dilation of the three-horns. Cases related to aqueduct stenosis presented with ependymal rupture and wall irregularities in advanced cases. Corpus callosum agenesis cases presented with small ventricular volumes, thin shape, normal or slightly enlarged anterior and inferior horns with dilation restricted to posterior horn. Cases related to trisomy 18 and

cytomegalovirus presented irregular ventricular walls associated with anomalous ventricular shapes, suggesting parenchymal destruction.

Conclusion Ventricular morphology evaluation gives important information on etiology of ventricular enlargement, supporting prognosis prediction and decision making process of the affected fetuses and their families.

Keywords Fetuses · Ventriculomegaly · Morphology · Etiology · Three-dimensional ultrasonography · Magnetic resonance imaging

Introduction

The fetal ventricular system size is an important marker of central nervous system (CNS) development that can be properly evaluated by obstetric sonography through abdominal and transvaginal route [1]. Ventricular dilations are among the most frequent cerebral abnormalities diagnosed during the prenatal period, occurring in isolation or being only the first sonographic sign of a whole set of structure deviations of the fetal CNS [2, 3].

The causes of ventriculomegaly (VM) are multiple and even though the isolated forms are relatively frequent, this is a condition associated with congenital malformations (anomalies of both the CNS and non-CNS) and acquired conditions as maternal infections, cerebral hemorrhage, intracranial tumors and maternal trauma that often result in a poor prognosis [4].

Sonography is the best tool to study and understand the pathology and developmental changes of the fetal central nervous system (CNS). Volume scanning (3D sonography) allows us to obtain images in all three classic scanning planes giving us the ability to view the brain through

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serial sections in any desired plane of our choice. Several post-processing features available also assist in highlighting pathology that may not be otherwise obvious [5]. Among the roles of fetal neurosonography is the inspection and characterization of the cerebral ventricles, which has proved to be one of the most diagnostically powerful and prognostically important features of the antepartum ultrasound (US) examination [6]. The classic measurement of the lateral ventricles is performed in an axial view of the fetal brain (transventricular plane) at the level of the atria, just over the choroid plexus glomus.

Atrial width is reported to remain constant throughout the second and third trimesters of gestation (mean diameter of $7.6 \text{ mm} \pm 0.6$) and values over 10 mm (97th percentile) is considered abnormal, leading to the diagnosis of VM [7]. However, the atrial width assesses only the posterior part of the lateral ventricle, providing only diagnosis information of VM, without etiologic or prognostic details [8].

The recognition of ventricular abnormality, however, must proceed from a precise understanding of the normal ranges of size and shape.

Once the ventricular dilatation processes are dynamic and occur in a distinct way according to the subjacent etiology, atrial width seems to be insufficient to represent reliably the progressive and non-simultaneous change in shape and size of lateral ventricles in VM, as well to inform about the causes and prognosis of VM [9, 10]. In this study, our aim was to evaluate lateral ventricles morphology of VM/hydrocephaly fetuses using three-dimensional ultrasonography (3DUS) rendering by virtual organ computer-aided analysis (VOCAL) technique and magnetic resonance imaging (MRI) and verify morphologic patterns related to etiology.

Methods

This was an observational cross-sectional study conducted in the Three-dimensional ultrasonography Sector of the Fetal Medicine Discipline of the Department of Obstetrics and the Imaging Diagnosis Department, Federal University of São Paulo (UNIFESP) from July 2008 to April 2009. The study was approved by the local ethics committee. Inclusion criteria comprised patients with singleton pregnancies between 20 and 36 gestational weeks with fetal diagnosis of ventriculomegaly (atrial width $>10 \text{ mm}$). After signing the post-informed consent, patients were included to the study.

The patients underwent conventional and 3D neurosonography and to fetal MRI with an interval of at most 7 days between examinations as part of a research protocol for CNS abnormalities in our service. Sonographic assessment was performed in an Accuvix XQ device (Medison, Seoul, South Korea) equipped with a convex volumetric multifrequency probe (4.0–7.0 MHz) and MRI in 1.5 T

superconducting system model Sonata Maestro Class (Siemens Medical Solutions, Erlangen, Germany) with 43-mT gradient, with dedicated 8 channel phased-array body coils. All data acquirement and 3D volumetric analysis were performed by a single observer (K.K.H.) skilled and experienced in fetal medicine and fetal neurology as well as MRI evaluations were made by a single radiologist (P.S.O.) experienced in the same field.

Ventricular morphological aspects studied were: shape, aspect of the three ventricular horns (anterior, posterior, inferior), wall irregularities and deformities and presence of points of rupture of fusion of the ventricles. All findings were correlated with the underlying cause of ventriculomegaly. Pearson correlation coefficient (r) was calculated to estimate the level of correlation between 3D-sonographic and MRI estimated volumes and findings.

Three-dimensional ultrasonography

3DUS images were acquired based on coronal views of the fetal brain in order to minimize reverberation artifacts, through the anterior fontanel always when possible. The preset used was: sweep angle $60\text{--}80^\circ$, high to maximum resolution (velocity low), edge enhance 3 and frequency: resolution. All data sets were post-processed using rotational method (VOCAL) in the 30° mode (chosen arbitrarily) as described by Raine-Fenning et al. [11]. The 34 lateral ventricles were assessed successfully with determination of ventricular volume and three-dimensional rendering of each studied structure at the end of the process. The “cine” mode allowed viewing of the rendering ventricle by different angles. 34 lateral ventricles were assessed, with ventricular volume determination and three-dimensional rendering of each studied structure at the end of the process. We evaluated 34 fetal lateral ventricles with ventricular volume determination and the realization of three-dimensional rendering the end of the process. The use of the “cine” mode allowed visualization of all ventricular surfaces.

Magnetic resonance imaging

All examinations were performed in the morning period. Maternal fasting was requested in order to avoid fetal movements during the exam (reducing motion MRI artifacts). No maternal sedation was needed. The patients chose either the supine or lateral positioning (either head-first or feet-first in the magnet) to minimize claustrophobia. The MRI protocol used was: section thickness of 4 mm; Fourier factor of 0.625; FOV between $280 \times 280 \text{ mm}$ and $350 \times 350 \text{ mm}$ (varying with gestational age); pixel of $1.3 \times 1.6 \text{ mm}^2$; bandwidth of 391 Hz/pixel and matrix of 256×256 . T1 and T2 [Spin echo-based half-Fourier

acquisition single-shot turbo spin-echo (HASTE) and gradient echo-based steady-state free precession (true FISP)] weighted sequences were obtained in the three orthogonal planes (axial/sagittal/coronal). Radiological analysis was performed with quantitative and qualitative assessment of fetal intracranial structures. Ventricular volume was estimated using T2-weighted coronal images in the Leonardo workstation using ARGUS VA60C software (Siemens AG, Erlangen, Germany).

Results

Mean gestational age of enrolled patients was 29 weeks and 3 days (range 24–35 weeks). All studied cases presented fetal ventriculomegaly, uni or bilateral secondary to different etiologies. There was a high prevalence of neural tube defects/Arnold–Chiari type 2 syndrome and aqueduct stenosis in our sample (29 and 23%, respectively). Two cases were secondary to fetal infection (cytomegalovirus and

rubella), confirmed by PCR of the amniotic fluid. One case of aqueductal stenosis was related to misoprostol use in first trimester, leading to Möebius syndrome.

Chromosomal analysis was performed in 52% of the cases, with only one abnormal result (trisomy 18). All patients were submitted to syphilis (VDRL), hepatitis B (ELISA), toxoplasmosis (IgG, IgM, IgG avidity) and rubella (IgG, IgM) tests during gestation. 59% (10/17) also had tests for CMV (IgG, IgM).

One case presented with intrauterine fetal demise in week 34 (trisomy 18) and 2 cases with early perinatal death (Möebius syndrome and congenital rubella: 10 and 40 min of life, respectively). Table 1 demonstrates sample characteristics, diagnosis, chromosomal analysis results and perinatal outcome.

There were no surprises related to clinical presentation of the cases on birth. Case 1 (Möebius sequence) was confirmed due to facial signs associated to aqueductal stenosis; Case 11 (trisomy 18) had all features of the classic syndrome including severe IUGR, clenched hands, low ear

Table 1 Gestational age at examination, chromosomal analysis, diagnosis and perinatal outcome

Case	GA at US/MRI (weeks)	Diagnosis (US and MRI)	Chromosomal analysis	Immediate perinatal to first week of life outcome
1	28	Aqueductal stenosis: Möebius sequence	46, XY	C-section 32w, 1,685 g, Apgar 3/3, neonatal demise (40" necropsy unauthorized)
2	30	Arnold–Chiari type 2 syndrome	46, XY	C-section 34w, 2,895 g, Apgar 7/9, neurosurgery first week
3	32	Aqueductal stenosis	NP	LFU
4	29	Aqueductal stenosis	46, XX	NL 38w, 2,520 g, Apgar 9/10, VP shunting
5	24	Infectious fetopathy (cytomegalovirus)	NP	LFU
6	27	Arnold–Chiari type 2 syndrome	46, XX	LFU
7	25	Aqueductal stenosis	46, XX	NL 36w, 2,960 g, Apgar 9/10, VP shunting
8	33	Arnold–Chiari type 2 syndrome	NP	C-section 37w, 3,190 g, Apgar 3/8, neurosurgery first week, VP shunting
9	33	Dandy–Walker complex	NP	C-section 35w, 2,870 g, Apgar 8/9
10	34	Tetraventricular VM + Arachnoid cyst	NP	NL 40w, 3,625 g, Apgar 9/9
11	28	Trisomy 18: Edwards syndrome	47, XY, +18	IUFD 34w, NL (necropsy unauthorized)
12	33	Corpus callosum agenesis + NMD	46, XY	C-section 36w, 2,385 g, Apgar 8/9
13	29	Arnold–Chiari type 2 syndrome	46, XY	C-section 38w, 3,560 g, Apgar 6/8, neurosurgery first week
14	35	Megacisterna magna	NP	LFU
15	25	Mild isolated unilateral ventriculomegaly	NP	NL 39w, 3,450 g, Apgar 9/10
16	28	Congenital rubella syndrome (with rachischisis)	46, XX	C-section 34w, 1,450 g, Apgar 1/1/0 (neonatal demise), (necropsy unauthorized)
17	25	Arnold–Chiari type 2 syndrome	NP	C-section 36w, 2,120 g, Apgar 8/9, neurosurgery first week

US sonography, MRI magnetic resonance imaging, Apgar APGAR score, NP not performed, NL normal labor, LFU lost of follow-up, VP ventriculoperitoneal, w weeks, g grams, IUFD intrauterine fetal demise, MV ventriculomegaly, NMD neuronal migration disorder

implantation, bilateral club feet, facial anomalies; Case 12 (callosal agenesis) had microcephaly, scoliosis and club feet, Aicardi syndrome could not be ruled out; Case 16 did not present classically as congenital rubella syndrome, although confirmed fetal infection and normal karyotype: rachischisis, club feet, single umbilical artery, low implantation and deformity of ears, diaphragmatic hernia, clinodactyly, micrognathia.

Regarding ventricular characteristics, Arnold–Chiari fetuses had moderate to severe global ventricular dilatation, regular walls and angulated shape of the frontal horns. Aqueduct stenosis frequently presented with ependymal and cavum septi pellucidi rupture, besides wall irregularities. Lateral ventricles showed a ballooning shape with prominent dilatation of the body and posterior horn. These cases were associated with bigger estimated volumes than obtained in VM by other causes assessed by both methods (Table 2).

In callosal agenesis the estimated ventricular volume was very small and its shape thinner and stretched, with slit like anterior and inferior horns and mildly dilated posterior horn, compatible with the term colpocephaly typical of this condition. In trisomy 18 and fetal infections by cytomegalovirus and rubella ventricular walls were extremely irregular following no characteristic pattern, ventricular asymmetry was pronounced and intraventricular hemorrhage was frequent. Periventricular parenchymal disruption and cysts were also present. Figure 1 presents a sample of the 3D-sonographic rendering (virtual ventricular models)

Table 2 Ventricular volumes estimated by three-dimensional ultrasonography (3DUS) and magnetic resonance imaging (MRI) (bigger ventricle)

Case #	Volume 3DUS (cm ³)	Volume MRI (cm ³)
1	83	86
2	65	62
3	73	74
4	48	50
5	63	70
6	8	8
7	25	30
8	32	33
9	42	44
10	10	9
11	16	18
12	8	9
13	21	22
14	14	11
15	4	3
16	6	8
17	30	29

compared to MRI images, related to different etiologies. Sonographic findings were reassured by MRI images, with elevated concordance of the morphologic findings ($r = 0.99$) and estimated ventricular volumes between the two methods ($r = 0.84$ for the right ventricles and 0.90 for the left ventricles; $p < 0.05$).

Discussion

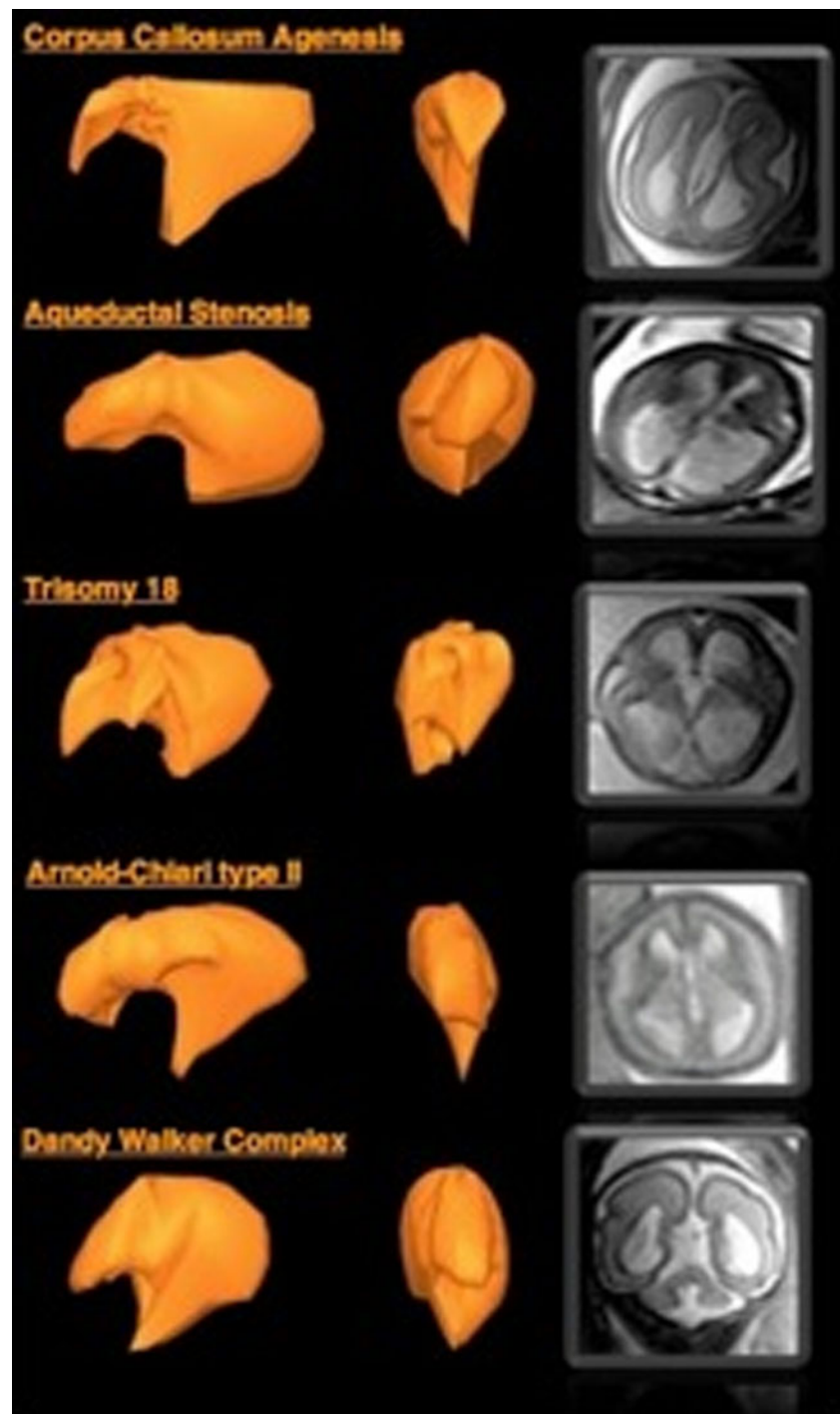
Normal and abnormal developmental processes of the human brain can already be assessed and followed during intrauterine life through non-invasive diagnostic methods as ultrasonography and fetal MRI. Abnormality of the size or morphology of the fetal cerebral ventricles has profound and ominous implications for the prognosis of the fetus, with increased morbidity and perinatal mortality. Ventricular dilatations are evolutive events that occur in a specific way related to the underlying cause as seen in aqueduct stenosis, for example, when posterior horn and ventricular body enlargements occur first and the anterior horn is undertaken at last [12]. These observations of the ventricular dynamics brings us the belief that only the classic atrial width measurement in axial view of the brain cannot reliably demonstrate its progressive changes in shape and size that occur non-simultaneously [13]. It is an excellent screening method, though insufficient to determine prognosis and evolutive stage. Conversely, the evaluation of morphology of the ventricles is often a valuable indicator of underlying pathology in cases of in utero CNS pathology [14].

The prevalence of ventriculomegaly in São Paulo is 2.6:1,000 live born children and the study of ventriculomegaly in Brazil is especially important because national laws do not allow termination of pregnancy in cases of fetal malformation, even in very severe lesions [15]. In our country, these children will be born leaving fetal medicine, neonatal and pediatric staffs to deal with this pathology in a multidisciplinary approach to provide suitable medical assistance and improve their quality of life and their families.

So far, no single morphometric or functional factor has precisely predicted perinatal prognosis [16]. As prognosis is related to extent of the dilatation, associated anomalies and, more importantly, the underlying cause of VM, prenatal accurate diagnosis is crucial to appropriate assistance [17].

According to Gilmore et al. [18] great part of the initial studies on ventricular measurement by bidimensional sonography have significant limitations, as low resolution of the images of the brain structures proximal to the transducer and inconsistent anatomic localization in ventricular atria measurement. In their study on ventricular volumetric assessment of neonates using 3DUS the authors suggest that with a better comprehension of lateral ventricles' morphology and actual size we possibly could

Fig. 1 3D rendering of lateral ventricle by VOCAL method of five fetuses with different causes of ventriculomegaly: frontal and lateral ventricular view (*left and center*). Correlation with ventricular aspect in MRI: T2-weighted axial and coronal views (*right*). VOCAL: virtual organ computer-aided analysis, MRI: magnetic resonance imaging



identify high-risk patients for neurodevelopment impairment, proving that this method allows the accomplishment of valid measurements of lateral ventricles in these patients, besides these values being comparable to those obtained by MRI. The rates of false-positive diagnosis of VM based on atrial width can get to 12% due to measurement errors [19].

Levine et al. [20] compared 2D-sonography with MRI in the assessment of ventricular morphology and emphasize

the importance of visualizing the entirety of the lateral ventricles in the study of fetuses with mild ventriculomegaly. And this is especially important in cases of callosal agenesis and digenesis, as unless an image of the frontal horns is obtained, these conditions with mild atria dilatation will continue to be missed.

Cases secondary to similar pathophysiological mechanisms (obstructive VM, midline abnormalities, cerebral disruptions, neuronal migration disturbances) showed the

same morphological ventricular pattern, varying only in volume sizes and symmetry aspects. In our study, an angular configuration of the frontal horns was seen only in association with spina bifida which agrees with Rickard et al. [14] and Levine et al. [20]. This finding can therefore serve as a valuable secondary sign of the presence of neural tube defects. Ventricular contours differ with different diagnoses of CNS abnormalities. The analysis of the frontal horn views presents itself very important and imperative to establish final diagnosis, as demonstrated by Bennett et al. [21] in a case series of fetal callosal agenesis.

Ventriculomegaly secondary to an obstruction of the cerebrospinal fluid pathways presented global ventricular dilatations and stood for the biggest estimated volumes, intraventricular hypertension being the possible cause of neurological impairment in those patients due to compression and ischemia of the surrounding brain parenchyma. In ex-vacuum ventricular dilatations the amount of intraventricular fluid is not the agent of the pathological process, being variable in quantity and location according to the topography of the main related structural abnormality. These findings are demonstrated in a very satisfying way by the three-dimensional rendering that builds a “virtual cast” of the ventricular surface.

To the present moment, we are not aware of other studies that have used morphological information provided by 3DUS rendering using VOCAL method compared to MRI in fetal ventriculomegaly assessment.

In summary, ventricular morphology evaluation gives important information in addition to the single conventional measurement of the atria on etiology of ventricular enlargement, supporting prognosis prediction and decision making process of the affected fetuses and their families.

Conflict of interest None.

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