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MATERNO-FETAL MEDICINE

Congenital hydrocephalus: gestational and neonatal outcomes

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Abstract
Purpose To evaluate gestational and neonatal outcomes in pregnancies complicated by fetal hydrocephalus.
Methods Retrospective analysis of 287 cases of fetal hydrocephalus followed at the Fetal Medicine Unit of the University of Campinas in the period of 1996 to 2006.
Results Mean maternal age was 25 years, mean gestational age at diagnosis was 27 weeks. There were 50 cases of isolated ventriculomegaly, 95 cases of Chiari II malformation and 142 cases of ventriculomegaly associated with other malformations. Preterm delivery and vaginal delivery were more frequent in the group of ventriculomegaly associated with other malformations. Cardiac, skeletal and renal malformations were the most common associated malformations. Cesarean section was common (95%) in the Chiari II group. Fetal and neonatal death occurred more frequently (29 and 68%, respectively) in the group of ventriculomegaly associated with other malformations. Chromosomal anomalies were present in 15% of 165 investigated cases.
Conclusions Fetal and neonatal prognosis and outcome are associated with the presence of associated anomalies and aneuploidy.

Keywords Congenital hydrocephalus · Fetal ventriculomegaly · Chiari malformation · Prenatal diagnosis

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Introduction

Congenital hydrocephalus occurs in 1 in every 1,000 newborns [1]. It is a severe and common malformation, associated with significant fetal and neonatal morbidity and mortality. Prognostic factors are associated anomalies (intra and extracranial), aneuploidy, subjacent etiology and degree of ventricular enlargement [2, 3]. Prenatal findings can predict morbidity and mortality with relative accuracy. Ventriculomegaly is often used in synonymous to hydrocephalus, although some authors believe that hydrocephalus should be restricted to ventriculomegaly associated with disturbances within the liquor channel system [4].

This retrospective study describes the clinical experience of a fetal medicine unit with prenatal evaluation and follow-up of congenital hydrocephalus. It also analyzes factors associated with short-term neonatal prognosis. The study was previously approved by the Ethics Board of our institution.

Methods

In the period ranging from 1996 to 2006, 314 cases with prenatal diagnosis of fetal ventriculomegaly were attended at the Fetal Medicine Unit. Of these, 27 cases were

excluded because of insufficient or unreliable data in the charts or because delivery occurred in another hospital. All fetuses were evaluated with sonographic examination by a fetal medicine specialist for certification of the diagnosis of ventriculomegaly (lateral atrium width at the level of the choroid plexus $\geq$10 mm). Prenatal karyotyping by amniocentesis or cordocentesis was offered and 165 analyses were performed. Maternal serological exams for toxoplasmosis, cytomegalovirus, rubella and syphilis were performed. Prenatal follow-up consisted of serial sonography and pregnancies were allowed to proceed to term unless maternal or fetal well-being was threatened.

Results

Mean maternal age was 25 years, ranging from 14 to 44 and 39% were primigravid. Mean gestational age at the time of diagnosis was 27 weeks ranging from 14 to 38 weeks.

Table 1 shows karyotype results (n = 165).

Among nine fetuses with trisomy 13, eight had holoprosencephaly. Two fetuses with Dandy–Walker malformation had chromosomal anomalies: one trisomy 21 and one triploidy. No chromosomal anomalies were found in fetuses with Chiari II malformation.

Serological evaluation for toxoplasmosis showed positive IgM antibodies in four women (3.7% of 214), fetal brain infarction and necrosis were seen in three of these cases. Because sonographic findings were highly suggestive of infection and late gestational age at referral, no fetal blood samplings were performed. No positive IgM for rubella was found in 182 samples. There was also no case of syphilis or acute cytomegalovirus infections.

The overall fetal death rate was 19.7% (61 cases). The overall neonatal death rate (before hospital discharge) was 23% (52 of 226 liveborns). The combined fetal and neonatal death rate was 39.4% (113/287).

Table 2 shows a comparison of gestational and neonatal outcomes between isolated and non-isolated ventriculomegaly. Non-isolated ventriculomegaly group had significantly higher rates of fetal and neonatal death. In the isolated ventriculomegaly group, rates of fetal and neonatal death were 6 and 13%, respectively. No differences were found when comparing cesarean delivery, abnormal karyotyping and preterm delivery rates.

Table 3 shows the most frequent anomalies associated with ventriculomegaly.

Facial malformations were the most frequent anomalies associated, followed by intracranial findings. Dandy–Walker malformation was found in 24 cases (8.3%), holoprosencephaly in 23 (8%), corpus callosum agenesis in 17 (5.9%), microcephaly in 11 (3.8%) and iniencephaly in 5 cases (1.7%). Three fetuses had intracranial hemorrhage detected, two prenatally and one at autopsy, all of them died. One had multiple severe malformations, one had achondrogenesis type II (Langer–Saldino) and one died after intra-partum cephalocentesis because of severe macrocrania.

There were 14 cases of unilateral ventriculomegaly. Among 10 karyotypes analyzed, there was one trisomy 21 and nine normal. Four died in the neonatal period because of severe associated malformations (arthogriposis, achondrogenesis), and two had intracranial hemorrhage.

In 164 patients, there was at least one initial measurement of the width of atrium of the lateral ventricle: 28 had 10–12 mm, 23 had 12–14 mm and 113 had 15 mm or more. Main outcomes in these groups are summarized in Table 4.

Neonatal ventricular shunting with valve placement was performed in 47 newborns, 6 died while still in the neonatal intensive care unit. Shunting was placed in 29 newborns with Chiari II malformation.

Consanguinity was reported by one couple, they were first degree cousins. The fetus had Fallot's tetralogy, ileal atresia and severe ventriculomegaly, and had severe neurological handicap in the short-term follow up.

Table 1 Prenatal karyotyping results of 165 fetuses with hydrocephalus

Karyotype	Frequency *n* (%)
46 XY	56 (34)
46 XX	84 (51)
Trisomy 21	5 (3)
Trisomy 13	9 (5.4)
Trisomy 18	2 (1.2)
Turner	1 (0.6)
Others	8 (4.8)
Total	165

Table 2 Comparative analysis of main outcomes in isolated and non-isolated hydrocephalus

	Isolated (%)	Non-isolated (%)	RR	IC	*P*
Fetal death	6	22	4.32	1.2–10.9	**<0.05**
Neonatal death	13	58	3.55	1.2–15.9	**<0.05**
Cesarean delivery	69	72	0.96	0.8–1.2	>0.05
Abnormal karyotype	6	14	2.2	0.5–9.1	>0.05
Preterm delivery	27	33	1.22	0.7–2.1	>0.05

Bold values indicate statistical significance

Table 3 Frequency of associated anomalies in 287 fetuses with hydrocephalus

Type of malformation	Frequency *n* (%)
Facial	58 (20.2)
Intracranial	47 (16.4)
Cardiac	36 (12.5)
Skeletal	25 (8.7)
Renal	22 (7.7)
Others	47 (16.4)

Discussion

This is one of the largest samples of fetuses with hydrocephalus reported as a single center experience. Unlike North America and Europe, termination of pregnancy for non-lethal malformations is not legally accepted in Brazil. Our experience included mildly and severely affected cases and allowed us to perform consistent counseling regarding a severe short-term prognosis and reduced chances of prolonged survival for the most severe cases.

Etiological investigation for fetal hydrocephalus classically includes screening for congenital infections, chromosomal analysis and more recently magnetic resonance imaging (MRI). Anti-platelet antibodies should be searched when intracranial hemorrhage is found. Rarer conditions, like fetal ischemic stroke, are more difficult to diagnose.

Infections are a known cause of ventriculomegaly [3, 5]. There are controversies surrounding routine screening for infections, mainly cytomegalovirus, toxoplasmosis, rubella, syphilis and herpes [3]. In a recent series of 20 cases of severe ventriculomegaly, one patient tested positive for toxoplasmosis IgM [6]. In another series of 30 cases, two patients also tested IgM positive [3], which brings an incidence of 5–6.6%. Serological exams showed low positivity rate and poor diagnostic performance in our sample. Toxoplasmosis was not diagnosed with certainty in any patient. It was extremely difficult to make a precise diagnosis, mainly due to the late gestational age at referral (mean 27 weeks) and in those cases, positivity for IgM or avidity test may not be useful and even PCR might have gestational age-related high false-negative rates [7]. The evidence for prenatal treatment of toxoplasmosis for the prevention of serious consequences, such as hydrocephalus, was recently disputed [8]. Treatment starts very late in many cases, when transmission and lesions have already occurred. However, three out of four fetuses whose mothers had serological evidence of possible acute infection (IgM positive) had severe intracranial findings, consistent with toxoplasmosis lesions and two of them died. These patients also had a late referral, and early screening was not performed. Although no pathognomonic lesion of toxoplasmosis has been described, hydrocephalus with maternal seroconversion is highly suggestive in these cases. CMV and rubella were not diagnosed in any patient by maternal antibody screening. In a series of 64 cases, 3 patients (4.7%) had serological evidence of CMV infection [2]. Herpes virus is a known neurotropic virus and a potential etiologic agent, associated with severe brain lesions like hydranencephaly and microcephaly when occurring in the first 20 weeks of pregnancy [9]. Isolation and confirmation of fetal herpetic infection is not an easy task and is not routinely performed.

Although some authors report rates of fetal infection as high as 23% associated with ventriculomegaly [3], serological investigation for infection-associated hydrocephalus needs to be prospectively studied in a systematic and standardized approach, maybe with more aggressive tools, such as polymerase chain reaction in amniotic fluid or fetal blood. A diagnosis of infection-associated hydrocephalus, besides having prognostic value, is very important for counseling, since recurrence is extremely rare for immune-competent patients.

The incidence of chromosomal abnormalities was similar to that reported in literature. Aneuploidy significantly worsens fetal and neonatal prognosis and karyotyping is extremely important in fetuses with associated anomalies. The positive likelihood ratio for non-isolated and isolated ventriculomegaly is 7 and 2, respectively, for trisomy 21 [10]. In isolated cases, 8% had chromosomal anomalies, a frequency slightly higher than that reported in larger series [11] and lower than that reported in smaller series [2].

Table 4 Main outcomes related to initial lateral ventricle atrium width measurement in 164 cases

Outcome	Lateral ventricle atrium width (mm)		
	10–11 ($n = 28$)	12–14 ($n = 23$)	≥15 ($n = 113$)
Ventriculomegaly progression	11 (39.3%)	18 (72.2%)	39 (79.1% or 39/48 with at least 2 measurements)
Abnormal karyotype	0 (9/9)	2 (16.6% or 2/14)	2 (4.8% or 2/44)
Perinatal mortality	9 (32%)	7 (30.4%)	25 (22.1%)
Associated anomalies	6 (21.4%)	7 (30%)	53 (46.1%)
Frequency of neonatal ventricular shunting	12%	12%	76%

In our sample the degree of ventriculomegaly did not predict the risk of chromosomal abnormalities, in agreement with other reports [3]. Abnormal karyotypes were more common in fetuses with initial lateral atrium width between 12 and 14 mm (16.6%). Extracranial structural anomalies more than doubled the risk of aneuploidy, but this difference did not reach statistical significance. Holoprosencephaly was strongly correlated to aneuploidy, and this finding confirms the general concept that karyotyping is mandatory in these cases [10]. Although a consensus has not emerged regarding routine chromosomal analysis for isolated ventriculomegaly and since aneuploidy is a strong risk factor for adverse outcome, it seems appropriate to offer karyotyping.

There were three detected cases of intracranial bleeding. Two had additional severe malformations and one developed severe macrocrania. None of them was tested for antiplatelet antibodies. The incidence of fetal hemorrhage is around 16% for fetuses knowingly affected by platelet alloimmunization [12], but there is no data on the incidence of antiplatelet antibodies in fetuses with hydrocephalus. Given the severity of the condition and the potential for treatment and prevention for future pregnancies, it seems justifiable to search for antiplatelet antibodies in mothers of fetuses with unexplained hydrocephalus associated with intracranial hemorrhage, whether prenatally or postnatally diagnosed [13].

Associated structural anomalies significantly worsened prognosis, and fetal and neonatal death were much more frequent in this group. A thorough search for other anomalies must be carried out, since it might have a great impact in counseling.

Chiari II malformation is a group with specific characteristics. These fetuses rarely have chromosomal abnormalities (none occurred in our sample) and their prognosis depends on the upper level of the spinal lesion and the degree of ventricular enlargement [14, 15]. Our high rate of cesarean section in this group is justified on the basis of a policy of scheduled delivery and early neurosurgical intervention, although no clear benefit of cesarean over vaginal delivery has been conclusively demonstrated so far [16].

Magnetic resonance imaging was recently added (since 2007) to our investigation protocol because a number of reviews have pointed that this imaging modality is very useful, especially for central nervous system malformations [17]. We did not perform routine MRI in the sample studied in this paper.

A weakness in our study is that we did not have a systematic protocol of investigation for ventriculomegaly in the early years of our fetal medicine unit. This has led us to mount a heterogeneous data bank, with incomplete diagnostic work-up and follow-up of several cases, in some of them also because of late gestational age at referral. Ultrasonographic measurement of the lateral ventricle width was not made in all cases, which precluded us to make more detailed analysis. However, due to the large number of cases, valuable information was collected.

Another important aspect that deserves attention is long-term prognosis and prospective studies are needed, evaluating associated morbidity and quality of life in survivors. Published literature focuses almost exclusively on isolated, borderline or mild ventriculomegaly and there is a lack of studies of more severe cases.

Pregnancies affected by fetuses with hydrocephalus should be managed in tertiary care referral centers with fetal medicine teams. The complexity of the diagnostic and therapeutic approaches, specific issues like mode of delivery, neonatal care and prognosis prompt a multidisciplinary team with expertise in many fields such as ultra-sonography, radiology, neurosurgery, pediatric intensive care, obstetrics, genetics, nursery and psychology. Our study shows that severe ventriculomegaly has a very poor prognosis, with extremely high rates of fetal and neonatal loss. Associated anomalies worsened prognosis significantly, increasing rates of fetal and neonatal death. Although abnormal karyotype did not reach statistical significance regarding fetal and neonatal death, this might be due to the small number of cases.

Counseling parents in prenatal care is important, especially in our country where termination of pregnancy is not legally accepted. End-of-life decisions in neonatal intensive care units are very painful, and provision of psychological care must be carried out once the diagnosis is confirmed.

Conflict of interest statement None

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