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Severe Fetal Hydrocephalus with and without Neural Tube Defect: A Comparative Study

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Key Words
Hydrocephalus · Lateral ventricles · Cerebral ventriculomegaly · Neural tube defects · Ultrasonography, severe hydrocephalus

Abstract
Objective: To describe the main perinatal and 1-year outcomes in babies with a prenatal ultrasonographic diagnosis of severe hydrocephalus according to the presence or absence of a neural tube defect (NTD) in a country where abortion is illegal. ***Method:*** The study population consisted of cases referred to and delivered at Hospital de Clínicas de Porto Alegre, diagnosed between January 1993 and December 2001. The diagnosis of severe hydrocephalus was based on a lateral ventricular atrium diameter ≥15 mm in at least one hemisphere. ***Results:*** Sixty cases were ascertained: 28 with NTD (group 1) and 32 without NTD (group 2). The groups were similar in terms of maternal and child variables at birth and hospitalization days during the 1st year of life. The mortality (including intrauterine deaths and deaths of babies with malformations incompatible with life that characterize a very poor prognosis) until 1 year of age was 36% in group 1 and 59% in group 2 (p = 0.077). The rate of cardiac malformations was higher in the group without NTD (p = 0.015). The length of hospital stay after birth (1st admission) was significantly higher in the group with NTD (p = 0.007). ***Conclusions:*** The morbidity was higher in the group with NTD, possibly due to the higher number of surgical interventions in the central nervous system. However, the mortality was higher in the group without NTD, possibly due to the presence of other associated malformations, especially congenital heart disease. Further studies should focus on neurological function and quality of life of the children and their families at the end of the 1st year and after 2 or 6 years of age.

Introduction

Fetal hydrocephalus is a relatively common congenital malformation, with a prevalence of between 8 and 20 per 10,000 live births [1, 2]. Hydrocephalus is caused primarily by neural tube defects (NTD), including meningocele, myelomeningocele, and encephalocele [1]. In these cases, there is a defect in the covering of the central nervous system (CNS), with exposure of neural elements through the spine or skull, distorting the system's architecture, obstructing the circulation of cerebrospinal fluid, and

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causing hydrocephalus. Cases of hydrocephalus that are not associated with NTD include a wide range of etiologies, such as infection and chromosomal, genetic, and multifactorial syndromes [1].

The ultrasonographic diagnosis of fetal hydrocephalus is possible starting at 15 weeks of gestational age and involves the measurement of the cross-sectional diameter of the lateral ventricular atrium [3–6]. Severe hydrocephalus has been defined as a diameter ≥15 mm [6].

The prognosis of fetal CNS malformations is usually poor, but depends on etiology and degree of involvement [7, 8]. Neurological impairment has been described in up to 80% of the cases, ranging from mild to severe. Perinatal and neonatal mortality rates have been reported to reach 38% [9–17].

The considerable number of elective abortions described in the literature due to severe congenital hydrocephalus (50% or higher) impacts the data concerning the natural history of this malformation [9–14], which remains largely unknown. In our country, however, abortion is illegal, and it is not allowed even in the presence of conditions such as hydrocephalus. This provides us with the opportunity to more closely observe the survival rates and the perinatal outcomes in newborns with hydrocephalus.

Therefore, the objective of the present paper was to describe the perinatal and 1-year outcomes in babies with a prenatal ultrasonographic diagnosis of severe hydrocephalus with or without NTD. These two groups were compared in terms of the rate of cardiac and other associated malformations; final diagnosis of infants with severe fetal hydrocephalus; intrauterine, neonatal, and 1-year mortality; maternal and child variables at birth; length of hospital stay after birth; number of surgical interventions in the CNS, and hospitalization days during the 1st year of life.

Patients and Methods

The study population consisted of cases referred to and delivered at the Hospital de Clínicas de Porto Alegre, diagnosed with severe fetal hydrocephalus with or without NTD between January 1993 and December 2001. Data regarding prenatal course and postnatal outcomes were abstracted from the medical records. Cases prior to January 2000 were retrospectively identified, while those within the last 2 years of the study were consecutively enrolled.

The diagnosis of severe hydrocephalus (ventriculomegaly) was based on a lateral ventricular atrium diameter ≥15 mm in at least one hemisphere. The width of the lateral ventricle was measured from the medial border to the lateral atrial border immediately next to the choroid plexus and cross-sectionally to the septum pellucidum [4].

All patients underwent ultrasound (fetal anomaly scan) for confirmation of the findings on which the referral was based. The gestational age was defined preferentially based on the date of the last menstrual period. If there was disagreement of more than 1 week between the date of the last menses and the ultrasonographic fetal biometric data, the gestational age was calculated based on the earliest ultrasonography available. All ultrasonographic examinations were performed by two authors (D.S. and J.A.M.) and later reviewed by one of them (J.A.M.).

Serial sonographic evaluations were performed on average every 2 weeks. Fetal echocardiographic examinations were performed after 18 weeks of pregnancy. All patients were offered maternal serology for investigation of toxoplasmosis, syphilis, rubella, cytomegalovirus, and herpes simplex (TORCH) as part of the routine prenatal investigation of fetal hydrocephalus. Amniocentesis was indicated to obtain the karyotype in patients with malformations that were not part of the myelomeningocele sequence, but it was performed only if the mother consented. If there was any clinical/serological evidence of maternal infection, the amniotic fluid was also submitted to polymerase chain reaction for toxoplasmosis, cytomegalovirus, herpes simplex, and rubella research.

After birth, the babies were followed by a neuropediatrician, in accordance with the Hospital's protocol. The mothers were offered a prenatal and/or postnatal consultation with a geneticist to identify any associated clinical syndromes. In addition, the mothers were advised in terms of folic acid use in future pregnancies to prevent the occurrence of NTD. Babies born in other hospitals were excluded.

The following outcomes were evaluated: an identifiable clinical syndrome (including, but not limited to, chromosomal syndromes), cardiac malformations, other associated major and minor malformations, evidence of an infectious etiology at birth, intrauterine death, gestational age at birth, birth weight, 1- and 5-min Apgar scores, length of hospital stay after birth and number of surgical interventions in the CNS (ventriculoperitoneal shunts and/or shunt revisions, myelomeningocele closure, or reintervention due to wound dehiscence or skin necrosis), and hospitalization days and mortality during the 1st year of life.

The data were entered into an Access database for later analysis using the Statistical Package for the Social Sciences. Measures of central tendency were described using mean values and standard deviation for data with symmetric distribution and median and interquartile range for data with asymmetric distribution. Student's t test was used for continuous variables, the Mann-Whitney test for independent samples, and Fisher's exact test for categorical variables. The level of significance was established at 5% ($p < 0.05$). The study was approved by the Hospital de Clínicas de Porto Alegre Research Ethics Committee.

Results

During the 9 years covered by the study, 64 patients were diagnosed with severe fetal hydrocephalus. Four cases were delivered elsewhere and were excluded. Thus,

Table 1. Characteristics of the study sample

	Group 1 with NTD (n = 28)	Group 2 without NTD (n = 32)	p
Maternal age, years	26.4 (SD = 6.6)	25.5 (SD = 7.4)	0.613
Number of pregnancies (interquartile range)	2 (1–3)	2 (1–4)	0.882
Number of abortions (interquartile range)	0 (0)	0 (0–1)	0.381
Gestational age at diagnosis, weeks	28.2 (SD = 5.5)	27.1 (SD = 5.9)	0.152
Baseline lateral ventricular atrium diameter, mm	21.8 (SD = 11.2)	23.7 (SD = 8.3)	0.469

60 cases of severe fetal hydrocephalus were considered. The patients were divided into two groups: group 1 included 28 cases associated with NTD, and group 2 included 32 cases without NTD.

The groups were similar in terms of maternal age, number of pregnancies, number of abortions, gestational age at hydrocephalus diagnosis, and baseline lateral ventricular atrium diameter (table 1). The following supplementary prenatal tests were performed: In group 1 (with NTD), 10 patients (36%) had their karyotype determined (1 case of 47,XY + fragment of unknown origin and 1 case of trisomy 18), 15 patients (54%) underwent fetal echocardiography (1 case of ventricular septal defect), and 20 mothers (71%) underwent TORCH investigation (normal in all cases). In group 2 (without NTD), 19 patients (59%) underwent karyotype determination (2 cases of trisomy 21), 16 patients (50%) underwent fetal echocardiography (abnormal in 8 cases, with 3 cases of interatrial communication, 2 cases of ventricular septal defect, 1 case of atrioventricular septal defect, 1 case of complex heart disease, and 1 case of interventricular septal hypertrophy), and 31 mothers (97%) underwent TORCH investigation (1 case of cytomegalovirus).

Final Diagnosis of Infants with Fetal Hydrocephalus and Associated Malformations

The final diagnosis of the patients in the two groups is described in table 2. In group 1, 11 of the 28 patients (39%) had some associated malformation versus 13 of the 32 patients (41%) in group 2 (p = 0.999). As shown in table 3, the most frequent malformation in group 1 was renal. The frequency of congenital heart disease was significantly higher in group 2 (p = 0.015, Fisher's exact test).

Perinatal Outcomes

Among the 28 patients in group 1, 4 had extracerebral malformations that were incompatible with life or were associated with a very poor prognosis: 1 case of diaphragmatic hernia (death at 12 h of life), 1 case of bilateral renal agenesis (death at 2 h of life), 1 case of bilateral renal dysplasia (stillbirth at 22 weeks of gestational age), and 1 case of trisomy 18 (unknown outcome). Of the remaining 24 patients, 2 (8%) were stillbirths (23 weeks of gestational age and fetal weight of 515 and 279 g, respectively) and were submitted to necropsy: 1 case of chest-lumbar NTD and 1 case of lumbosacral NTD associated with 47,XY and fragment of unknown origin.

In group 2, 6 patients had malformations that were incompatible with life: 1 case of diaphragmatic hernia (death at 24 h of life), 1 case of bilateral renal agenesis (stillbirth at 30 weeks of gestational age), 1 case of osteogenesis imperfecta (stillbirth at 33 weeks of gestational age), and 3 cases of nonimmune fetal hydrops (stillbirth at 30 and 35 weeks of gestation, respectively, and 1 case with unknown outcome). Of the remaining 26 patients, 6 (23%) were stillbirths with 5 being submitted to necropsy (mean gestational age 28 weeks, mean fetal weight 1,531 g): 2 cases of isolated hydrocephalus, 2 cases of trisomy 21 associated with heart disease, 1 case of multiple malformations (omphalocele + cleft palate) and 1 case of Pallister-Hall syndrome.

Excluding the babies with extracerebral malformations that were not compatible with life, there were no statistical differences between the groups in terms of intrauterine deaths (2 of 24 in group 1 vs. 6 of 26 in group 2; p = 0.250) and immediate perinatal outcomes in the 22 and 20 live newborns in groups 1 and 2, respectively (gestational age, Apgar score, and birth weight; table 4).

One-Year Follow-Up

Of the 22 babies in group 1, 4 (18%) died before reaching 1 year of age; in group 2, 7 out of the 20 babies (35%) died before 1 year of age (table 5). The groups were similar in terms of deaths before 1 year of age, survival, num-

Table 2. Final diagnosis of infants with severe fetal hydrocephalus

	Group 1 with NTD (n = 28)		Group 2 without NTD (n = 32)	
	n	%	n	%
Isolated NTD	18	64.3		
Isolated high NTD (encephalocele)	3	10.8		
Multiple malformations with normal karyotype	2	7.1[a]	1	3.1[d]
Chromosomal anomaly	2	7.1[b]	2	6.3[c]
Bilateral renal agenesis/dysplasia	2	7.1	1	3.1
Diaphragmatic hernia	1	3.6	1	3.1
Isolated severe hydrocephalus of unknown cause			12	37.4
Dandy-Walker syndrome			3	9.4
Nonimmune fetal hydrops			3	9.4
Genetic syndromes (Pallister-Hall and Walker-Warburg)			2	6.3
Arachnoid cyst			2	6.3
Intracranial hemorrhage			2	6.3
Aqueductal stenosis			1	3.1
Infection (cytomegalovirus)			1	3.1
Osteogenesis imperfecta			1	3.1

[a] One case with anorectal malformations + single umbilical artery and 1 case with bilateral cleft lip + single umbilical artery + dysplastic ears with auricular appendage.
[b] One case of 47, XY + fragment of unknown origin and 1 case of trisomy 18.
[c] Two cases of trisomy 21.
[d] Omphalocele + cleft palate.

Table 3. Malformations associated with severe fetal hydrocephalus

	Group 1 with NTD (n = 28)	Group 2 without NTD (n = 32)	Total
Major malformations			
Congenital heart disease	1	8	9 (15%)
Kidney[a]	4	1	5 (8%)
Cleft palate	1	2	3 (5%)
Diaphragmatic hernia	1	1	2 (3%)
Omphalocele	1	1	2 (3%)
Polydactyly	0	1	1 (2%)
Minor malformations			
Single umbilical artery	3	2	5 (8%)

[a] Including single kidney, bilateral renal agenesis, and bilateral renal dysplasia.

ber of readmissions, and number of hospitalization days during the 1st year of life. The duration of hospital stays after birth (first admission) was longer in group 1 in comparison with group 2 ($p < 0.05$). Similarly, the number of surgical interventions (ventriculoperitoneal shunts and/or shunt revisions, myelomeningocele closure, or reintervention due to wound dehiscence or skin necrosis) was also significantly higher in group 1 than in group 2 ($p < 0.05$; table 5).

In group 1, the 22 babies born alive were submitted to myelomeningocele closure at a median age of 8 h (range 4–22.5 h). Concerning ventriculoperitoneal shunt, in group 1, this procedure was performed in 17 of the 22 patients (77%) at a median age of 21 (range 13–44) days. Myelomeningocele closure and/or ventriculoperitoneal shunt were associated with complications in 17 of the 22 patients. In group 2, 11 of the 20 patients (55%) underwent ventriculoperitoneal shunt at a median age of 7 (range 3–19) days ($p = 0.192$), and procedure-associated complications were observed in 6 of these 11 patients (54.5%). The difference between the groups concerning procedure-associated complications was not significant ($p = 0.240$). The most frequent complications in group 1 were surgical wound dehiscence or necrosis (8/17, 47%), ventriculitis (5/17, 29%), and shunt obstruction (3/17, 18%). In group 2, 3 of the 6 patients (50%) had ventriculitis.

Table 4. Perinatal outcomes in live newborns

	Group 1 with NTD (n = 22)	Group 2 without NTD (n = 20)	p
Gestational age at birth, weeks	37.4 ± 9.4	36.7 ± 12.9	0.194[a]
Apgar score at 1st min (interquartile range)	8 (4–8)	7 (5–8)	0.888[b]
Apgar score at 5th min (interquartile range)	9 (8–10)	9 (7–9)	0.205[b]
Weight, g	2,989.1 ± 383.9	3,375.2 ± 966.7	0.091[a]

[a] Student's t test.
[b] Mann-Whitney test.

Table 5. Outcome of severe fetal hydrocephalus until 1 year of age

	Group 1 with NTD (n = 22)	Group 2 without NTD (n = 20)	p
Death <1 year	4 (18.2%)	7 (35%)	0.298
Median survival, days (interquartile range)	66 (17–287)	6 (2–101)	0.588
Survivors	18 (81.8%)	13 (65%)	–
Length of first admission, days (interquartile range)	44 (31–67)	26 (15–32)	0.007[a]
Number of surgical interventions (interquartile range)	2 (2–3)	1 (0–2)	0.007[a]
Number of readmissions (interquartile range)	1 (0–2)	1 (0–2)	0.984
Median hospitalization days in 1st year (interquartile range)	58 (37–87)	37 (23–59)	0.089

[a] Mann-Whitney test.

Discussion

The prognosis of congenital hydrocephalus has been shown to vary widely due to the different degrees of ventriculomegaly [12, 14, 18] and the broad spectrum of etiologies [7, 8, 11, 13, 14]. It is important to underscore that many prognostic studies define ventriculomegaly based on the lateral ventricle/hemispheric width ratio [18–21]. However, the low accuracy of this method to reveal the true ventricular size has led to its gradual replacement, since the 1980s, with the lateral ventricular atrium diameter as the criterion to diagnose ventriculomegaly [3–5, 22]. In the present work, only cases of severe hydrocephalus (i.e., those that would be associated with the worst prognosis) were included (lateral ventricular atrium diameter ≥15 mm). A comparison with other prognostic studies must take into consideration the possible differences in terms of degree of ventriculomegaly and diagnostic criteria.

The single most common etiology for congenital hydrocephalus is NTD which affects 30–60% of the cases [11, 13, 14]. In this study, 47% of the cases were associated with NTD. Congenital hydrocephalus not associated with NTD may have various causes. Beke et al. [8] have divided the origin of hydrocephalus into infectious (47%), brain malformations (20%), and intrauterine hemorrhage (10%). We observed these etiologies in 3, 19, and 6% of our patients, respectively. Gaglioti et al. [14] have reported an infectious etiology in 23% of the cases (cytomegalovirus and toxoplasmosis). However, in that study, only 30 out of 176 cases (17%) were tested for TORCH (infection identified in 7 patients) versus 31 out of 32 cases without NTD in the present study (1 case of CMV). According to Partington [7], infectious congenital hydrocephalus occurs in not more than 10% of the cases, a result which is more similar to what we observed. It should be noted that the fact that not all of our patients underwent a full evaluation (e.g., for karyotype and infectious disease workup) is a limitation of this study.

The prognosis is also associated with the presence of other malformations [9, 13, 14, 20, 21] and with the progression of ventriculomegaly [11, 20, 23]. In the present

study, about 40% of the cases had associated malformations. The prognosis of fetuses with severe hydrocephalus without NTD was worse, since they had a higher proportion of associated malformations (41 vs. 39%), especially congenital heart disease (50 vs. 7%) when compared with the fetuses with NTD.

The mortality that we observed during the 1st year of life (including intrauterine deaths and deaths of babies with malformations incompatible with life) was very high: 36% in the group with NTD and 59% in the group without NTD ($p = 0.077$; Fisher's exact test). The neonatal mortality was 18% in the group with NTD, similar to that of previous reports (7–21%) [15–17]. The neonatal mortality was 35% in the group without NTD which is also in agreement with findings reported in the literature (21–38%) [10, 12, 14, 24]. There seems to be a nonsignificant (probably due to the small sample size) trend suggesting that intrauterine death (19 vs. 7%) and death during the 1st year of life (35 vs. 18%) are more frequent in the group without NTD in comparison with the group with NTD.

The duration of hospital stay after birth was significantly longer in the group with NTD due to the larger number of surgical interventions. In this group, 77% of the patients were submitted to ventriculoperitoneal shunt (median age 21 days), whereas in the group without NTD, 55% of the patients were submitted to this procedure (median age 7 days). In the literature, 70–90% of the patients have been reported to require a ventriculoperitoneal shunt in the 1st year of life (mean age 21–49 days) [11, 19, 25]. The complications related to surgery (shunt or surgical closure of myelomeningocele) were similar in both groups (77% in group 1 and 55% in group 2) and associated with infection in 29 and 50% of the patients, respectively, showing agreement with findings of previous studies [17, 26, 27]. Tuli el al. [26] observed a failure rate of 64% with ventricular peritoneal shunts, and this was due to infection in 24% of the cases. Sbragia et al. [17] reported a 39% surgical complication rate in fetuses with closure of myelomeningocele, a rate below our finding of 77%. This probably resulted from the inclusion of less severe cases of ventriculomegaly in that study (86% of the cases of myelomeningocele associated with ventriculomegaly vs. 100% in the present study). According to Caldarelli et al. [27], a higher degree of ventriculomegaly implies a higher incidence of obstructive and infectious complications. In the present study, the median number of surgical interventions was two (group 1) and one (group 2) during the 1st year of life. Kirkinen et al. [18] reported a mean of 5.6 new surgeries per patient in 10 years of follow-up (SD = 3.3).

Prenatal myelomeningocele intervention has been studied with the objective of decreasing the need for ventriculoperitoneal shunt after birth and improving the prognosis associated with the loss of distal neurological function that occurs in fetuses with myelomeningocele. Bruner et al. [28] have compared the outcomes in 29 cases of intrauterine myelomeningocele repair versus 23 controls and suggested that intrauterine repair decreases the need for ventriculoperitoneal shunts (59 vs. 91%; $p = 0.01$) in newborns with spina bifida. In a more recent study carried out at the Vanderbilt University Medical Center [28], 178 fetuses underwent intrauterine repair of spina bifida, and 116 fetuses were followed until at least 1 year of age. 61 of these 116 fetuses (54%) required a shunt before turning 1 year. However, that study will only be completed within 3–4 years.

The efficacy of future treatments for fetal hydrocephalus can only be evaluated, if we learn more about this disease, still largely unknown. Nevertheless, the natural history of a disease can only be determined if its course or outcome is not interrupted. In that sense, the present study, carried out in a country where abortion is illegal, provides enlightening data. In addition, the present data are useful for prenatal counseling concerning this pathology.

In conclusion, the groups with and without NTD in this study were similar in terms of maternal and child variables at birth and hospitalization days during the 1st year of life. Children with severe hydrocephalus and NTD seem to have a poorer perinatal prognosis as compared with those without NTD. This is probably related to the higher number of surgical interventions. However, the mortality in the 1st year of life is higher (although not significantly) in children without NTD, possibly due to the higher number of associated malformations. Further studies should focus on the neurological function and quality of life of the children and their families at the end of the 1st year and after 2 or 6 years of age.

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