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Correlations between Ultrasound and Pathology in Fetal Ventricular System Anomalies

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Additional information is available at the end of the chapter

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Abstract

A total of 113 cases of fetal hydrocephalus with a lethal outcome (FHLO) from the Embryo-Fetopathologic Clinic at the Center for Maternity and Neonatology, Tunis, Tunisia and Obstetrics and Gynecology Clinic at St. George EAD University Hospital, Plovdiv, Bulgaria were studied, 86 of which had syndrome malformations: neural tube defects (NTDs)—29.2%, chromosomal abnormalities—23.9%, skeletal dysplasias—9.8%, VACTERL association—5.3%, Dandy-Walker malformation—3.4%, Other—14.2%. Risk factors for FHLO are miscarriages (odds ratio (OR): 19.500; confidence interval (CI): 4.020-94.594), stillbirths (OR: 10.897; CI: 1.169-10.564) and previous birth of a malformative child (OR = 5.385; CI: 1.385–18.896). FHLO is significantly associated with a maternal age over 40 years and third degree consanguinity of the fetus (OR = 18.500; CI: 1.146–298.547). The trisomies in our study were 27 (23.9%) and are significantly associated with an age above 38 years and FHLO (OR = 13.689; CI: 3.952–52.122). In medical abortion, stillbirth, or neonatal death, a fetopathological study enriches our knowledge of malformations, complements and completes the ultrasound examination, modifies genetic counseling, and determines the medical behavior in subsequent pregnancies. Also, associated risk factors and fetopathological changes in FHLO must be studied to increase the ultrasound prenatal diagnosis success.

Keywords: congenital hydrocephalus, ultrasound, MRI, cerebral anomalies, risk factors

1. Introduction

Congenital hydrocephalus (CH) is a severe malformation which is often associated with other abnormalities. The prenatally diagnosed serious birth defects, especially those associated

with a high risk of premature death, stillbirth, or neonatal death, are often referred to as “lethal,” as it is assumed that their potential treatment will be unsuccessful, which is the basis for the decision for the interruption of pregnancy due to medical reasons [1, 2]. Depending on the clinical criteria used in the definition of the disease, its incidence varies from 1 to 32 per 10,000 live births [3]. An increase in the prenatal diagnosis of CH has been observed, whereas the incidence of stillbirths remains stable. The interruption of pregnancy due to medical reasons reduces by almost a half the rate of hydrocephalus in live births. Currently, prenatal ultrasound is able to visualize ventriculomegaly, which can be caused by a number of reasons. Knowledge of the risk factors associated with CH may increase the chances of an early prenatal ultrasound diagnosis. Animal experiments have found that a wide range of environmental factors can cause hydrocephalus. They include alcohol consumption, X-rays, infections, eating disorders, and exposure to chemicals during pregnancy [4]. It has been established that one gene (L1 of Xq28 encoded for L1CAM) is connected with CH in humans. Although X-linked CH has a frequency of about 2–7% of all cases, L1CAM is found in about 15% of sporadic cases [5]. L1CAM mutations are closely related to stenosis of the cerebral aqueduct, the major pathology causing hydrocephalus in these cases. Sipek et al., in their study of CH for the period 1961–2000 in the Czech Republic, found that a mother’s age of over 37 years was statistically significantly related to CH, unlike the study by Van Landingham et al. [4, 6].

2. Aim of the study

To study the prenatally ultrasound diagnosed ventriculomegaly by fetopathological autopsy in fetuses, which ended in interruption of pregnancy due to medical reasons, stillbirth, or neonatal death, by searching associated with the congenital hydrocephalus isolated or syndromic malformations as well as the eventual risk factors for their occurrence.

3. Materials and methods

A total of 113 fetuses with CH were studied whose outcome was lethal. One hundred and three of them were received over a period of 3 years (2006–2009) and autopsied at the Embryo-Fetopathologic Clinic at the Center for Maternity and Neonatology, Tunis, Tunisia, out of a total of 21,316 births. Ten of the cases were from the Obstetrics and Gynecology Clinic at St. George EAD University Hospital, Plovdiv, Bulgaria, during the year 2016 out of a total of 2104 deliveries. The incidence of fetal hydrocephalus with a lethal outcome (FHLO) in both centers is almost identical—4.8 and 4.9 per 1000 births.

The fetuses are the result of interruption of pregnancy due to medical reasons, spontaneous abortions, and stillbirths. The maternal and fetal data were collected from the obstetric history, and a classical autopsy was performed immediately following the expulsion of

the fetus, after authorization for macroscopic and microscopic examination. The autopsy includes observation, biometry of the fetus, and in situ examination of the body cavities. The examination of the brain was performed 6 months later, after conservation with 10% formalin. It began with biometrics, measurement of the biparietal and frontal-occipital diameters, and study of the relationship between ocular distance and eyelid length. After opening the cranial cavity, the meninx, brainstem, cerebellum, cerebral hemispheres, gyration, and morphology were observed. The biometry of the brain—weight and bitemporal and fronto-occipital diameters of the encephalon, and weight and transverse diameter of the cerebellum—was also studied. The ventricular system was examined by horizontal or vertical hemispheric slices until the central part of the lateral ventricle was opened. The presence, shape, and thickness of corpus callosum were examined. With a linear meter, the ventricular width in the central part was measured. At a width of more than 10 mm, ventricular dilatation was diagnosed as hydrocephalus and at a diameter of over 15 mm—major hydrocephalus. In each study, material was taken for histological examination of the cerebral cortex, cerebellum, brainstem, choroid plexus, and cerebral meninx. SPSS version 19 was used for the interpretation of the data. A descriptive analysis and χ^2 -analysis were used.

4. Results

- **Age structure of the mothers:** The age range of mothers carrying fetuses with FHLO was 21–43 years. Under 26 years of age were 24 mothers (22%), 27–35 were 64 (58%) and 36–50 years of age were 21 mothers (19.3%). The average age of the mothers was 29.5 ± 0.72 .
- **Number of previous pregnancies of the mothers:** Most of the mothers carrying FHLO had one previous pregnancy (38.1%), followed by mothers with two previous pregnancies (19.5%). The average number of previous pregnancies is 2.50 ± 1.808 , with a range of 1 to 5 pregnancies. There were no data for previous pregnancies for only 2.7% of the mothers.
- **Number of previous births of the mothers:** In the studied group, most of the mothers had one previous birth (36.6%), followed by mothers without previous births (31.3%). The average number of births is 1.24 ± 1.23 , with a range of 0–5.
- **Blood group of the mothers:** Data were collected for the mothers' blood groups, but unfortunately there is no information for about 21% of the mothers carrying a fetus with FHLO of the studied group. It is noteworthy that most of the mothers were of blood group O(+) – 36 (32.0%), followed by A(+) – 23 (over 20.0%).
- **Consanguinity:** In our study, 27.4% of the marriages were consanguineous, with those of first degree being 15.4%, those of second degree 8.3%, and of third 3.7%.

5. Risk factors

In the present study, 80 of the pregnancies (70.7%) were without risk factors, and only 33 (29.3%) were under the influence of such. The risk factors were grouped into three categories: obstetric risk factors from past events, risk factors due to diseases of the mother, and exogenous risk factors.

- 1. Obstetric risk factors.** This group includes spontaneous abortions—13 (11.5%), voluntary abortions—1 (0.9%), birth of a child with malformations—11 (9.8%), stillbirths—2 (1.8%), multifetal pregnancy—2 (1.8%), and multi-year sterility—4 (3.5%).
- 2. Endogenous risk factors.** The risk factors from the mother include maternal age, hypertension—1 (0.9%), diabetes mellitus—2 (1.8%), bronchial asthma—2 (1.8%), thalassemia—2 (1.8%), and epilepsy—3 (2.7%).
- 3. Exogenous risk factors.** Exogenous risk factors for the pregnancy include pregnancies carried in geographical areas near mines and underground mineral water deposits and consanguineous marriages. In our study, the pregnancies from geographic regions with mining and underwater mineral water deposits were 5 (4.4%). Supplementation with folic acid is mandatory in Tunisia and Bulgaria. There were no women without folic acid supplementation.

The term of pregnancy termination is presented in **Figure 1**. Most interrupted pregnancies are between the 20th and 24th gestational weeks. Six pregnancies were carried to birth.

Motives for pregnancy termination. Interruption of pregnancy due to medical reasons was performed in 87 cases (77%); spontaneous abortions were 13 (11.5%), and there was 1 voluntary abortion (0.9%). There were 2 live births (1.8%) and 2 stillbirths (1.8%). In eight of the cases (7%), there is no information on the motive for pregnancy interruption (**Figure 2**).

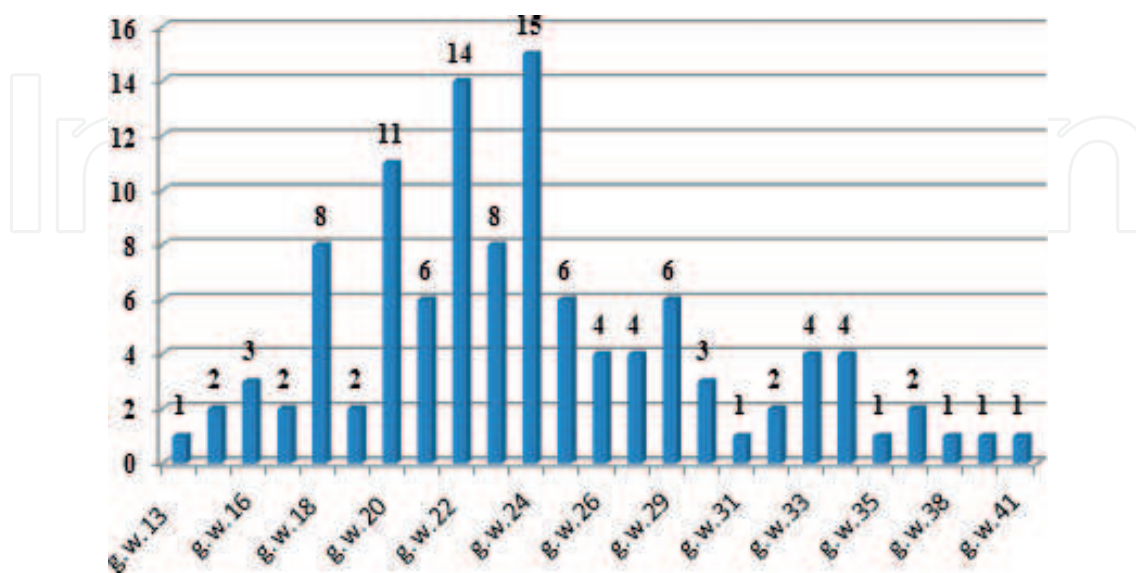


Figure 1. Term of pregnancy termination.

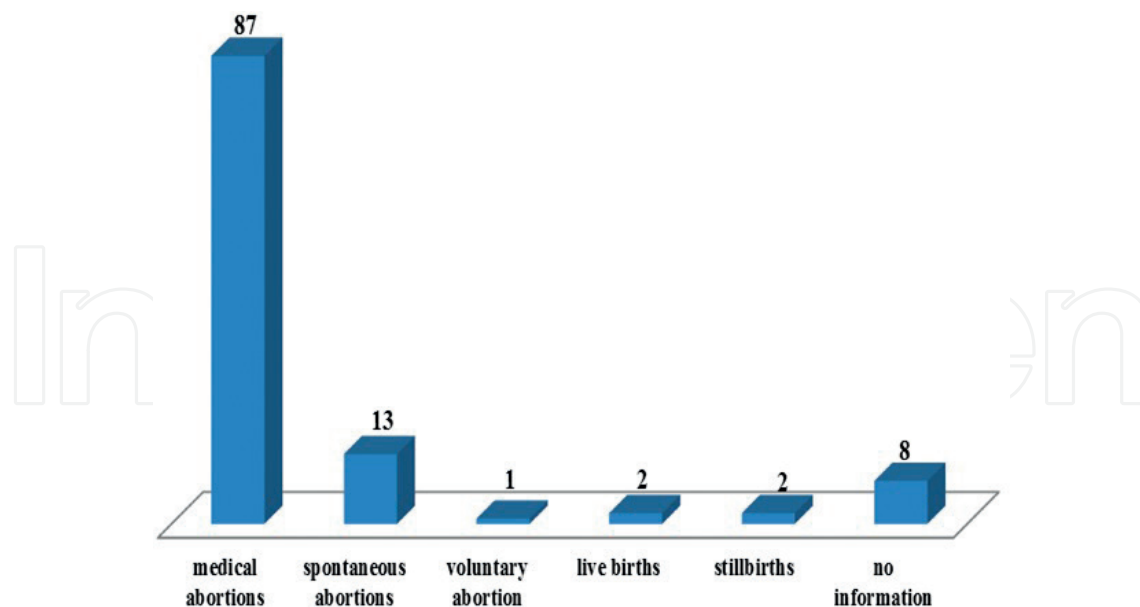


Figure 2. Motives for pregnancy termination.

6. Anthropometric characteristics of the fetuses

Distribution of lethal hydrocephalus by gender (sex ratio). The genders were equally affected, but the mean weight of male fetuses (842.17 ± 115.2) was less than that of female fetuses (892.06 ± 101.1), without the difference being statistically significant ($u = 0.51, p > 0.05$).

Age of the fetus. The average pregnancy term in the entire study is 24 ± 0.45 gestational weeks. The fetal expulsion in two-thirds of the cases occurred before the 24th gestational week, with the smallest fetus being 13 gestational weeks (Figure 1).

Fetus weight. The average weight of the fetuses is 865.99 ± 809.8 g with a range of 23–3800 g. It is worth noting that 50 fetuses (44.2%) weigh less than the corresponding gestational age.

7. System anomalies of the fetus

The head, extremities, and respiratory system anomalies associated with FHLO are presented in Table 1.

The cardiovascular system abnormalities are a total of 32 and are from all groups. The digestive system abnormalities are 56 and are broken down into groups: mesenteric (affecting the small intestine and colon), parenchymal (affecting the liver and spleen), anal imperforation (affecting the terminal part of the intestines), gall bladder agenesis, and situs inversus. The parenchymal and mesenteric abnormalities are evenly distributed. The gender abnormalities are present in both male and female fetuses with a ratio of female to male of 8:7. Hermaphroditism was established in four (3.5%) fetuses. The fatal hydrocephalus-associated anomalies of the cardiovascular, digestive, excretory, and genital systems are presented in Table 2.

Association of hydrocephalus with other brain abnormalities. In 85 fetuses (76%), hydrocephalus was associated with other brain abnormalities: polygyria—12 (10.7%); lissencephaly—2 (1.8%); agenesis of corpus callosum—18 (16%); agenesis of the cerebellar vermis—19 (16.9%); diastatomyelia—1 (0.9%); stenosis of the Sylvian aqueduct—5 (4.4%); holoprosencephaly—1 (0.9%) and cyst of the choroid plexus—2 (1.8%) (Table 3, Figure 4). The relations between the prenatal and postnatal diagnosis of hydrocephalus-associated brain abnormalities are shown in Figure 3.

The hydrocephalus-associated syndromes and malformations are presented in Table 4.

Systems	Types of anomalies	Anomalies	N/%
Lips, soft and hard palate	Clefts	Cleft lip	6/5.3
		Cleft palate	3/2.7
		Labia palate cleft	4/3.5
		Uvula cleft palate	1/0.9
	Configurations	High palate	25/22.1
	Total	39/34.5	
Anomalies of the nose	Configurations	Snub nose	4/3.5
	Agenesis	Arrhinia	1/0.9
	Atresia	Choanal atresia	1/0.9
	Total		6/5.3
Head and limb abnormalities	Head	Macrocrania	70/61.9
	Limb	Curved foot	23/20.4
	Agenesis	Short limbs	13/11.5
	Clinodactyly	Agenesis of finger	6/5.3
	Polydactyly	Finger clinodactyly	28/24.7
	Syndactyly		6/5.3
	Total		9/7.9
Anomalies of the respiratory system	Hypoplasia		182/161
	Incorrect lobulation		21/18.6
	Hypoplasia and		16/14.2
	Incorrect lobulation		6/5.3
	Situs inversus		2/1.8
	Liver agenesis		1/0.9
	Total		46/40.7

Table 1. Hydrocephalus-related abnormalities of the head, extremities, and respiratory system.

Most are neural tube defects followed by trisomies and skeletal dysplasias. The VACTERL association has been established in six fetuses (5.3%), four of which were male and two female, and the Dandy-Walker malformation in four fetuses (3.5%) (**Figure 4**).

The Meckel-Gruber syndrome, which is a ciliopathy, was established six times (5.4%). A karyotype study was performed on 23 fetuses (20.5%)—one by fluorescent in situ hybridization (FISH) and the rest by chromosome study. A magnetic resonance tomography (MRI) was performed in three cases.

Systems	Types of anomalies	Anomalies	N/%
Anomalies of the cardiovascular system	Position	Dextroradia	1/0.9
		Organomegaly	Cardiomegaly
	Defects	Atrial septal defect (ASD)	3/2.7
		Ventricular septal defect (VSD)	11/9.7
		Both together	2/1.8
		Tetralogy of Fallot	2/1.8
		Minor form of AV channel of the heart	2/1.8
		AV channel of the heart	2/1.8
	Stenoses	Aortic valve stenosis	1/0.9
		Pulmonary valve stenosis	1/0.9
	Transposition	Transposition of the great vessels (TGV)	1/0.9
	Isomerism	Isomerism of incoming vessels of the heart	3/2.7
	Hypoplasia	Hypoplastic right heart syndrome (HRHS)	1/0.9
	Total		32/28.3
Digestive system abnormalities	Mesenterial	Common mesentery	1/0.9
		Hemi-mesenter	22/19.5
	Parenchymal	Hepatomegaly	8/7.1
		Splenomegaly	3/2.7
		Hepato-splenomegaly	5/4.4
		Polysplenia	6/5.3
		Accessory spleen	1/0.9
	Imperforations	Imperforate anus	8/7.1
	Agensis	Gallbladder Agensis	1/0.9
	Situs inversus		1/0.9
	Total		56/49.5

Systems	Types of anomalies	Anomalies	N/%
Anomalies of kidney and urinary tract	Kidneys	Ptosis of the kidney	10/8.8
		Horseshoe kidney	4/3.4
		Agenesis (uni- and bilateral)	8/7.1
		Hydrophoresis	5/4.4
		Tubular necrosis	1/0.9
		Dysplasia	2/1.9
		Cystic dysplasia	6/5.3
	Urinary tract	Pelvicalyceal dilatation	4/3.4
		Megaureter	2/1.8
		Mega-bladder	2/1.8
		Hypoplasia of bladder	3/2.7
		Colovesical fistula	1/0.9
		Agenesis of ureter	5/4.4
		Total	53/46.9
Anomalies of the genitals	Female	Bicornuate uterus	5/4.4
		Ovarian hypoplasia	1/0.9
		Vaginal Atresia	1/0.9
		Hydrocolpos	2/1.8
	Male	Hypospadias	4/3.4
		Posterior urethral valve	1/0.9
		Cryptorchism	2/1.8
	Hermaphroditism	4/3.4	
	Total	19/16.8	

Table 2. Hydrocephalus-related abnormalities of cardiovascular, digestive, excretory, and genital systems.

The degree of hydrocephalus according to the fetopathological study is major hydrocephalus (hydrancephaly; >15 mm)—15 cases (13.3%) and ventriculomegaly (>10 mm)—77 cases (69%). Obstructive hydrocephalus as a result of intraventricular hemorrhage was found in 20 fetuses (17.7%) (**Table 5, Figure 4**).

The assessment of the significance of spontaneous abortions, abortions due to medical reasons, stillbirth, and a previous child with malformations as risk factors for the occurrence of hydrocephalus was accomplished by means of a χ^2 -analysis (**Table 6**).

The proportion of spontaneous abortion is almost four times higher, and the abortion due to medical reasons is more than four times higher, when compared to other risk factors for FHLO. Hydrocephalus is almost three times more likely to develop in cases of previous stillbirths in the obstetric history and more than two times more likely to occur in the presence

Brain associations	Number of cases	%
Polygyria	12	10.6
Lissencephaly	2	1.8
Agenesis of corpus callosum	18	15.9
Agenesis of cerebellar vermis	19	16.8
Cerebellar hypoplasia	25	22.1
Diastematomyelia	1	0.9
Aqueductal stenosis (stenosis of the aqueduct of Sylvius)	5	4.4
Holoprosencephaly	1	0.9
Choroid plexus cysts	2	1.8
Total	85	75.2

Table 3. Distribution of associated brain abnormalities with lethal hydrocephalus.

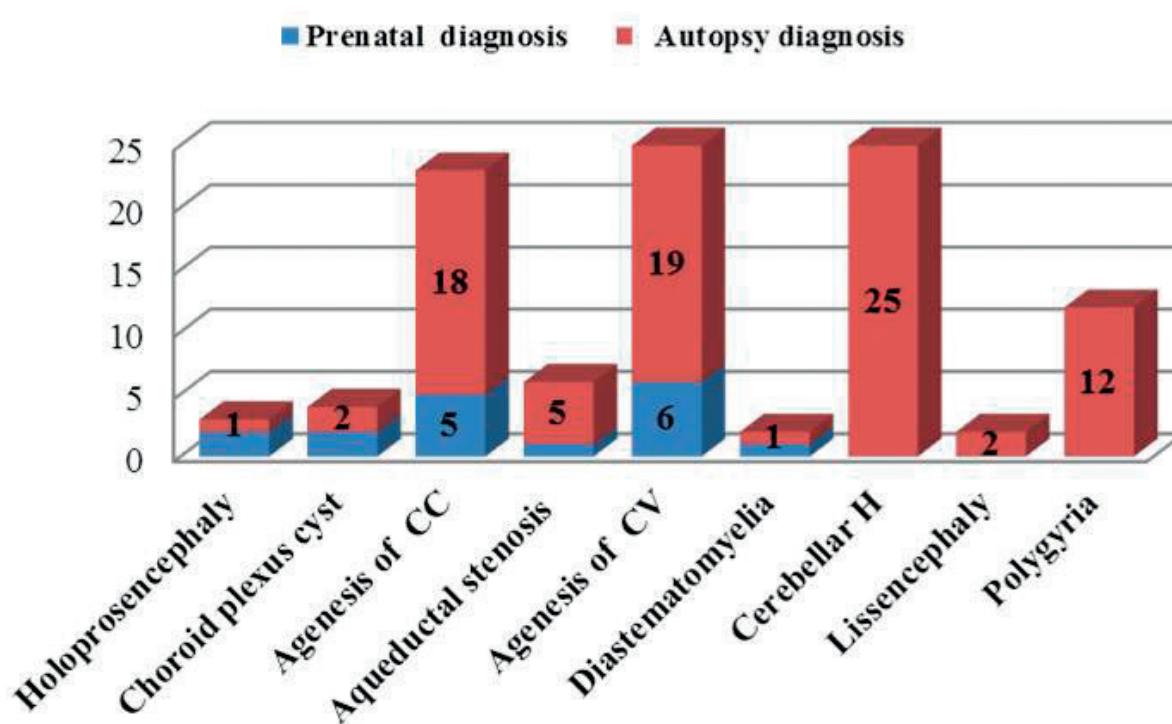


Figure 3. Relations between the prenatal and postnatal diagnosis of hydrocephalus-associated brain abnormalities. Abbreviations: CC, corpus callosum; CV, cerebeller vermis; H, hypoplasia.

of a pre-term birth of a child with a malformation, compared to the studied risk factors. The assessment of the significance of the different degrees of consanguinity in the presence of a child with malformations, epileptic mother, as well as the mother's age is shown in **Table 7**.

The incidence of FHLO is nearly six times higher when it is the result of a consanguineous marriage with a history of a previous pregnancy with a malformation, relative to the presence of hydrocephalus of a non-consanguineous marriage with no such a history. Almost 13 times higher is the incidence of FHLO in cases of maternal epilepsy with a consanguineous marriage of first degree (first cousins), when compared to the proportion of FHLO in a fetus

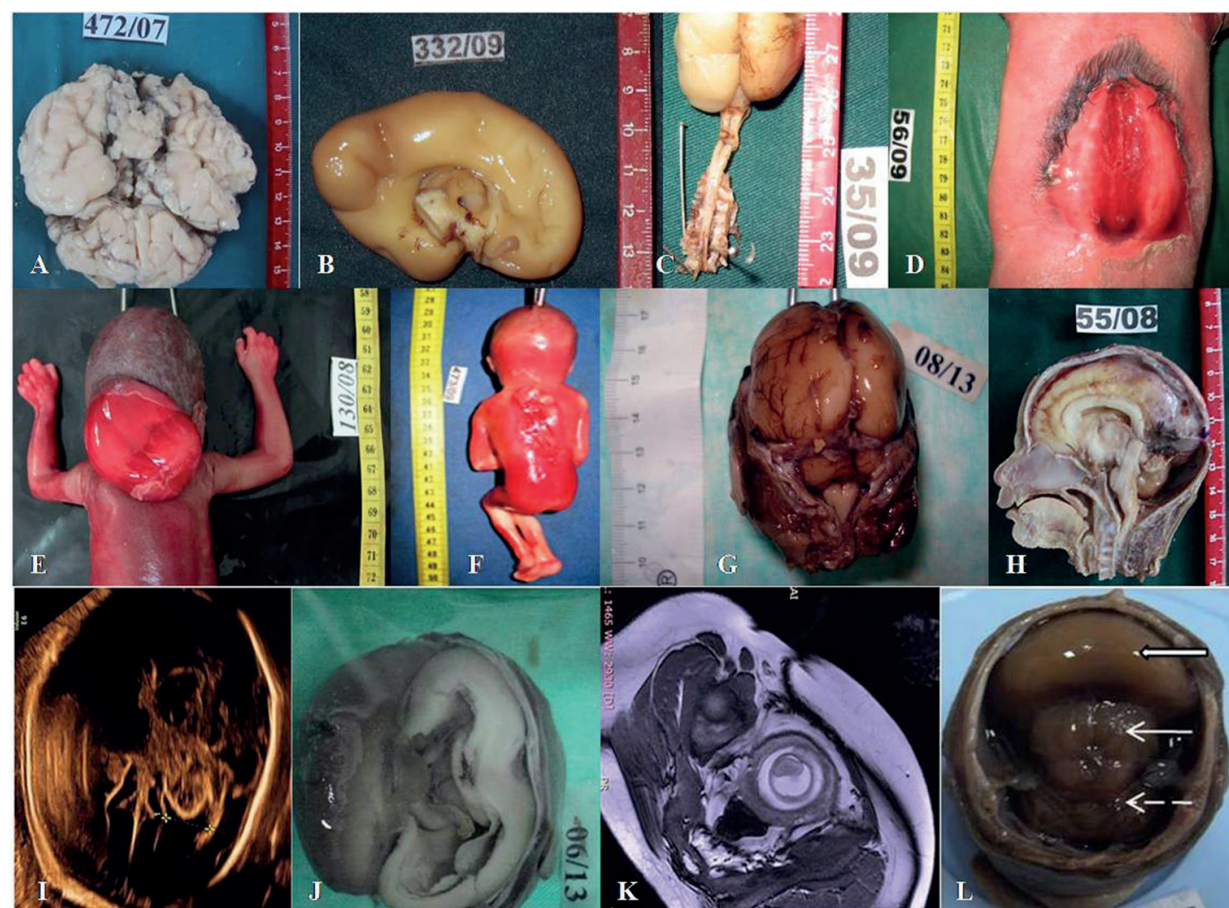


Figure 4. (A) Polygria (inferior view of the brain); (B) Agenesis of corpus callosum (medical view of hemisphere); (C) Extracted brain and spinal cord from the skull and vertebral canal. Split of the cord. Diastematomyelia; (D) Thoracolumbar spina bifida; (E) Occipital meningo-encephalocele; (F) Rachischisis; (G) Wedging of the cerebellar tonsils through the foramen magnum. Arnold-Chiari malformation; (H) Cystic dilatation of IVth ventricle, elevating of the tentorium, cerebellar hypoplasia. Dandy-Walker malformation; (I) Ventriculomegaly-ultrasound examination; (J) Ventriculomegaly (horizontal section of the right hemisphere); (K) Holoprosencephaly. Fetal MRI; (L) Holoprosencephaly. Fetal autopsy (White-black arrow—hemisphere, white arrow—brain stem, dotted arrow—cerebellum).

carried by an epileptic mother but not from such a marriage. Over four times higher is the proportion of FHLO in cases of consanguinity of second degree, when compared to hydrocephalus influenced by the other studied maternal risk factors. Almost four times higher is the proportion of FHLO with a maternal age between 27 and 35 years compared to other ages, with maternal risk factors present. The rate of hydrocephalus when the maternal age is over 40 years and with consanguinity of third degree is 13 times greater than women over 40 years of age without the risk factor consanguinity. The assessment of the degree of risk of consanguinity, the presence of spontaneous abortion, and the mother's blood group is presented in **Table 8**.

When the mother is from the A(+) blood group and has a consanguineous marriage (giving second-degree consanguinity in the fetus), FHLO has a two times higher incidence than in cases without consanguinity. Around two times higher is the incidence of FHLO, carried by mothers with O(+) blood group and a history of a previous spontaneous abortion,

Types of anomalies	Anomalies	N/%	
Neural tube defects	Spina bifida	10/8.8	
	Myelomeningocele	6/5.3	
	Encephalocele	6/5.3	
	Meningocele	6/5.3	
	Rachischisis	5/4.4	
	Total	33/29.2	
Chromosomal abnormalities	Trisomy 21	4/3.4	
	Trisomy 18	18/15.9	
	Trisomy 13	2/1.8	
	Trisomy 15	1/0.9	
	Trisomy 7 + 2	1/0.9	
	Triploidy	1/0.9	
	Total	27/23.9	
	Skeletal dysplasias	Ellis-van Creveld syndrome	1/0.9
		Thanatophoric dysplasia	3/2.7
Osteochondrodysplasia		1/0.9	
Osteogenesis imperfecta		2/1.8	
Arthrogryposis		3/2.7	
Total		10/9.8	
VACTERL association		6/5.3	
Dandy-Walker malformation		4/3.4	
Other syndromes and malformation	DiGeorge syndrome	1/0.9	
	Isomerism	3/2.7	
	Meckel-Gruber syndrome	6/5.3	
	Fraser syndrome	1/0.9	
	Fryns syndrome	1/0.9	
	Arnold-Chiari malformation	4/3.4	
	Total	16/14.2	

Table 4. Distribution of syndromes and malformations associated with lethal hydrocephalus.

compared to the occurrence when there is no such history. The degree of significance of the mother's age for the incidence of polygyria and abortions, obstetric and other risk factors, as well as the blood group for the occurrence of agenesis of the cerebellar vermis are shown in **Table 9**.

According to the degree of hydrocephalus	Number of cases	%
Major hydrocephalus (hydranencephaly)	15	13.3%
Ventriculomegaly	78	69.0%
Hydrocephaly due to intraventricular hemorrhage	20	17.7%
Total	113	100.0%

Table 5. Distribution of data on the extent and origin of hydrocephalus.

Indicators	Groups	Without risk factors		Risk factors		Total		χ^2	Fisher P	OR (CI)	
		N	%	N	%	N	%				
		Miscarriage	No	78	78	22	22				100
	There are	2	15.4	11	84.6	13	100.0				
	Total	80	70.8	33	29.2	11	100.0				
Abortion	No	78	81.3	18	18.8	96	100.0	33.727	0.000	32.500 (6.817–154.954)	
		There are	2	11.8	15	88.2	17				100.0
		Total	80	70.8	33	29.2	113				100.0
Stillbirth	No	79	73.1	29	29.6	108	100.0	6.529	0.011	10.897 (1.169–10.564)	
		There are	1	20	4	80	5				100.0
		total	80	70.8	33	29.2	113				100.0
Baby with malformation	No	76	75.4	26	25.5	102	100.0	6.988	0.008	5.385 (1.385–18.896)	
		There are	4	36.4	7	63.6	11				100.0
		Total	80	70.8	33	29.2	113				100.0

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2 , chi-square; P, sig.

Table 6. Risk factors and lethal hydrocephalus.

The association of FHLO and polygyria is more than three times higher in cases where the mother is over 35 years of age, when compared to cases with a mother's age less than 35 years. More than 2.5 times higher is the incidence of FHLO associated with agenesis of the cerebellar vermis in cases of a mother with a previous abortion, when compared to cases without a previous abortion. In the present study, the incidence of the association FHLO and agenesis of the cerebellar vermis is more than two times higher when exposed to the obstetric risk factors. Almost three times higher is the incidence of the association of FHLO and agenesis of the cerebellum in cases in which the mother's blood group is A(+), when compared to other maternal blood groups. The assessment of the importance of the

Indicators	Groups	No malformation				Baby with malformation		χ^2	Fisher <i>P</i>	OR (CI)
		<i>N</i>	%	<i>N</i>	%	<i>N</i>	%			
Consanguinity	No	74	96.1	3	3.9	77	100.0	9.768	0.002	7.309 (1.806–29.584)
	There are	27	77.1	8	22.9	35	100.0			
	Total	101	90.2	11	9.8	112	100.0			
Indicators	Groups	Without epilepsy		Epilepsy		Total		χ^2	<i>P</i>	OR (CI)
		<i>N</i>	%	<i>N</i>	%	<i>N</i>	%			
Consanguinity first degree	No	77	96.1	3	3.9	77	100.0	25.742	0.000	24.667 (5.189–117.247)
	There are	7	50.0	7	50.0	14	100.0			
	Total	84	89.0	10	11.0	94	100.0			
Indicators	Groups	Without risk factors		Risk factors		Total		χ^2	<i>P</i>	OR (CI)
		<i>N</i>	%	<i>N</i>	%	<i>N</i>	%			
Consanguinity second degree	No	71	93.4	5	6.6	76	100.0	4.014	0.045	75.680 (0.872–36.997)
	There are	5	71.4	2	28.6	7	100.0			
	Total	76	91.6	7	8.4	83	100.0			
Maternal age	Others	81	95.3	4	4.7	85	100.0	4.247	0.039	4.203 (0.977–18.601)
	27– 35 years	19	82.6	4	17.4	23	100.0			
	Total	100	92.6	8	7.4	108	100.0			
Indicators	Groups	Under 40 years of age		Over 40 years		Total		χ^2	<i>P</i>	OR (CI)
		<i>N</i>	%	<i>N</i>	%	<i>N</i>	%			
Consanguinity third degree	No	74	97.4	2	2.6	76	100.0	7.447	0.006	18.500 (1.146–298.547)
	There are	2	66.7	1	33.3	3	100.0			
	Total	76	96.2	3	3.8	79	100.0			

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2 , chi-square; *P*, sig.

Table 7. Consanguinity, risk factors, and lethal hydrocephalus.

maternal age for the association of hydrocephalus with trisomies, as well as the mother's blood group for the association of hydrocephalus and agenesis of corpus callosum is presented in **Table 10**.

The rate of FTLO associated with trisomy is more than six times higher when the mother's age is over 38 years of age, than in younger than 38-year-old mothers. Almost three times higher is the share of the association of FHLO with agenesis of corpus callosum in the fetus in cases of O(+) maternal blood group.

Indicators.	Groups	Another group		A+		Total		χ^2	P	OR (CI)
		N	%	N	%	N	%			
Consanguinity first degree	No	63	81.8	14	18.2	77	100.0	4.206	0.04	3.375 (1.010–11.279)
	First	8	57.1	6	42.9	14	100.0			
	Total	71	78.0	20	22.0	91	100.0			

Indicators	Groups	Another group		O+		Total		χ^2	P	OR (CI)
		N	%	N	%	N	%			
Miscarriage	No	74	74.0	26	26.0	100	100.0	4.315	0.038	3.321 (1.022–10.789)
	There are	6	46.2	7	53.8	13	100.0			
	Total	80	70.8	33	29.2	113	100.0			

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2 , chi-square; P, sig.

Table 8. Blood groups, risk factors, and lethal hydrocephalus.

Indicators	Groups	Without polygyria		Polygyria		Total		χ^2	P	OR (CI)
		N	%	N	%	N	%			
Maternal age	≤35	82	92.1	7	7.9	89	100.0	4.894	0.027	4.894 (1.094–13.94)
	≥35	15	75.0	5	25.0	20	100.0			
	Total	97	89.1	12	11.0	109	100.0			

Indicators	Groups	Without agenesis of cerebellar vermis		Agenesis of cerebellar vermis		Total		χ^2	P	OR (CI)
		N	%	N	%	N	%			
Abortion	No	83	86.5	13	13.5	96	100.0	4.886	0.027	3.483 (1.099–1.040)
	There are	11	64.7	6	35.3	17	100.0			
	Total	94	83.2	19	16.8	113	100.0			
Obstetric risk factors	No	71	87.7	10	12.3	81	100.0	4.432	0.035	2.905 (1.048–8.052)
	There are	22	71.0	9	29.0	31	100.0			
	Total	93	83.0	19	17.0	112	100.0			
Risk factors	No	47	90.4	5	9.6	52	100.0	3.898	0.046	3.463 (0.977–12.274)
	There are	19	73.1	7	26.9	26	100.0			
	total	66	84.6	12	15.4	78	100.0			
A+ blood group	No	78	86.7	12	13.3	90	100.0	3.830	0.050	2.844 (0.969–8.342)
	There are	16	69.6	7	30.4	23	100.0			
	Total	94	83.2	19	16.8	113	100.0			

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2 , chi-square; P, sig.

Table 9. Brain abnormalities, risk factors, and lethal hydrocephalus.

Indicators	Groups	Without trisomy		Trisomy		Total		χ^2	P	OR (CI)
		N	%	N	%	N	%			
Maternal age	≤38	88	90.7	9	9.3	97	100.0	20.518	0.000	13.689 (3.952–52.122)
	≥38	5	41.7	7	58.3	12	100.0			
	total	93	85.3	16	14.7	109	100.0			

Indicators	Groups	Without agenesis of corpus callosum		Agenesis of corpus callosum		Total		χ^2	P	OR (CI)
		N	%	N	%	N	%			
O+ blood group	No	53	86.9	8	13.1	61	100.0	4.441	0.035	3.614 (1.044–12.510)
	There are	11	64.7	6	35.3	17	100.0			
	Total	64	82.1	14	17.9	78	100.0			

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2 , chi-square; P, sig.

Table 10. Risk factors, trisomy, agenesis of corpus callosum, and lethal hydrocephalus.

8. Discussion

Currently, prenatal ultrasound is able to visualize ventriculomegaly. Knowledge of the risk factors associated with CH may increase the success of the prenatal ultrasound study. It has been established that a wide range of factors can cause hydrocephalus in animal experiments including alcohol consumption [7], X-ray [8], infections, food disorders, exposure to chemicals [9] and medications taken during pregnancy [10].

Our study is similar to those of Fernell et al., Stoll et al., and Porto et al. which showed that CH was significantly associated with previous abortions, stillbirth, and birth of a child with a malformation [11–13]. Our findings show that the risk of FHLO is increased in cases of previous spontaneous abortions (odds ratio (OR) = 19.500, confidence interval (CI): 4.020–94.594), stillbirth (OR = 10.897; CI: 1.169–10.564), and births of a child with a malformation (OR = 5.385; CI: 1.385–18.896). Pregnancy complications, such as an increase in the amniotic fluid over 1500 ml (polyhydramnios) or a reduction below 500 ml (oligohydramnios), are also considered as potential risk factors for CH [12, 13].

The role of consanguinity is also known for the occurrence of congenital malformations such as hydrocephalus, postaxial polydactyly of the hands, and defects of the lips and palate [13, 14]. In our study, FHLO is significantly associated with a maternal age over 40 years and third-degree consanguinity of the fetus (OR = 18.500; CI: 1.146–298.547). FHLO, previous pregnancies with malformations, and consanguinity are also significantly associated (OR = 7.309; CI: 1.806–29.584). FHLO with agenesis of the cerebellar vermis is significantly associated with the effect of obstetric risk factors (OR = 2.905; CI: 1.048–8.052).

Almost all studies have documented a slightly higher percentage of male fetuses in cases of CH in live births and stillbirths as well as in fetopathologic autopsies [15–18]. Van Landingham et al. did not find a difference in the genders of the children with hydrocephalus compared to the general population [4].

According to the study of Van Landingham et al. in 2009, the mother's age is not associated with CH, unlike the study by Sipek et al. for the period 1961–2000 in the Czech Republic which found that a mother's age over 37 years was significantly associated with CH [4, 6]. Hydrocephalus is significantly associated with a mother's age above 40 years and third-degree consanguinity, and it is 18 times higher compared to women above 40 years of age without consanguinity (OR = 18.500; CI: 1.146–298.547).

In regard to maternal disease, it is known that mothers suffering from diabetes mellitus have a significantly higher risk for giving birth to a child with congenital malformations, especially cardiovascular and neural tube defects [4, 19, 20].

Hydrocephalus is often divided by genetic specialists into a syndromic and non-syndromic form, depending on the presence of associated malformations [21, 22]. Some authors prefer to differentiate hydrocephalus in which the phenotype is characterized mainly with brain malformations and hydrocephalus which is associated with significant physical anomalies and clinical symptoms [23]. In cases with a specific clinical syndrome or genetic changes, hydrocephalus is best to be defined as hydrocephalus associated with the corresponding syndrome.

Some enzyme mutations result in defective neuron connections with the extracellular matrix, abnormal formation of the limiting glial membrane, and disturbances in the neuronal migration [24, 25]. As a result, characteristic brain malformation develops—loss of cerebral gyration, abnormal white matter of the hemispheres as well as brainstem anomalies (flat pons, enlarged tectum, and curved medulla oblongata), often associated with an aqueductal stenosis and cerebellar cysts. These findings often cannot be found by the prenatal examination, especially in cases of significant ventriculomegaly, making the MRI study essential [26]. In our study, the risk increases almost five times for the association of FHLO and polygyria when the mother's age is above 35 years (OR = 4.894; CI: 1.094–13.94). The association of FHLO and agenesis of the cerebellar vermis is significantly associated with previous abortions (OR = 3.483; CI: 1.099–1.040) and the effect of risk factors (OR = 3.463; CI: 0.977–12.274). Ventriculomegaly is significantly associated with agenesis of corpus callosum, as well as O(+) blood group of the mother, when compared to other blood groups (OR = 3.614; CI: 1.044–12.510). Hydrocephalus may be associated with other brain malformations such as holoprosencephaly, rhombencephalosynapsis, Aicardi syndrome, agenesis of corpus callosum, and periventricular heterotopia [27–31].

Some cytogenetic malformations are associated with hydrocephalus, including trisomy 13, 18, 21, and triploidy [32]. The trisomies in our study were 27 (24.1%) and their occurrence is significantly associated with a mother's age above 38 years (OR = 13.689; CI: 3.952–52.122).

NTD-associated hydrocephalus has a multifactor genesis. Experiments with animals have found that the intrauterine leak age of cerebrospinal fluid causes the Arnold-Chiari type II malformation, which causes an obstruction of the cerebrospinal fluid flow [33, 34]. Genetic mutations responsible for planar cell polarity such as Fuzzy (FUZ), VANGL1, and CELSR1 add to the development of NTDs [35–37]. Other mutations of genes with a relation to planar cell polarity (CELSR2 and MPDZ) may cause hydrocephalus regardless of the presence of NTDs [38, 39]. The specific pathogenetic mechanism is not completely clear, but it is accepted that a disjunction of the ependymal cilia is present [40]. The neural tube defects in our study were 33 (29.4%), with the most common being spina bifida, followed by myelomeningocele, encephalocele, and meningocele.

9. Conclusion

Congenital hydrocephalus with a lethal outcome is the result of a significant number of risk factors and is often associated with other malformations. Therefore, it is important to perform a prenatal ultrasound study in pregnancies with risk factors to diagnose possible CH or other malformations. Currently, the prenatal ultrasound is able to visualize ventriculomegaly and should be directed toward the search of other associated malformations, and when they are suspected, an MRI study and genetic testing must follow. In cases of medical abortion, stillbirth, or neonatal death, a fetopathological study must be carried out which enriches our knowledge of malformations, complements and completes the ultrasound examination, modifies genetic counseling, and determines the behavior to be followed when taking responsibility for a subsequent pregnancy. It is also important to further study the associated risk factors and the fetopathological changes in CH in order to increase the success of the ultrasound prenatal diagnosis.

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