Correlations between Ultrasound and Pathology in Fetal Ventricular System Anomalies

Tanya Kitova, Borislav Kitov, Denis Milkov and Aida Masmoudi

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 Ladingham 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,
gyrification, 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 $\chi^2$-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 pregnan-
cies (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 aver-
age 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 unfor-
tunately 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.](image)
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 ($t = 0.51$, $p > 0.05$).

**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%); diastamatomyelia—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       | Agenesia of finger| 6/5.3|
|                                      | Polydactyly        | Finger clinodactyly| 28/24.7|
|                                      | Syndactyly         |                   | 6/5.3|
|                                      | Total               |                   | 9/7.9|
|                                      |                     |                   | 182/161|
| Anomalies of the respiratory system  | Hypoplasia         |                   | 21/18.6|
|                                      | Incorrect lobulation|                  | 16/14.2|
|                                      | Hypoplasia and     |                   | 6/5.3|
|                                      | Incorrect lobulation|                  |       |
|                                      | 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                          | 2/1.8|
|                                  | 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 | 2/18 |
|                                  |                                       | 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 |
|                                  | Agenesis                              | Gallbladder Agenesis                  | 1/0.9 |
|                                  | Situs inversus                        |                                        | 1/0.9 |
|                                  | Total                                 |                                        | 56/49.5|
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 $\chi^2$-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

| 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 |
|                                              |                   | Megareter                          | 2/1.8 |
|                                              |                   | Mega-bladder                       | 2/1.8 |
|                                              |                   | Hydropoasia 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 Vaginal Atresia | 1/0.9 |
|                                              |                   | Hydrocolpos                        | 1/0.9 |
|                                              |                   |                                      | 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).

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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
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
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.
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.

| 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 |
|                               | Triplodia                  | 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.
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          | Without risk factors | Risk factors | Total | χ² | Fisher P | OR   (CI) |
|-----------------------------|-----------------|----------------------|--------------|-------|----|----------|--------|
|                             | N   | %     | N   | %     | N   | %     |       |        |
| Miscarriage                 | No  | 78    | 78  | 22    | 22  | 100   | 100.0 | 21.816|
|                             | There are      | 2     | 15.4| 11    | 84.6| 13    | 100.0 | (4.020–94.594) |
|                             | Total          | 80    | 70.8| 33    | 29.2| 11    | 100.0 |
| Abortion                    | No  | 78    | 81.3| 18    | 18.8| 96    | 100.0 | 33.727|
|                             | There are      | 2     | 11.8| 15    | 88.2| 17    | 100.0 | (6.817–154.954) |
|                             | Total          | 80    | 70.8| 33    | 29.2| 113   | 100.0 |
| Stillbirth                  | No  | 79    | 73.1| 29    | 29.6| 108   | 100.0 | 6.529 |
|                             | There are      | 1     | 20   | 4     | 80  | 5     | 100.0 | (1.169–10.564) |
|                             | 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 |
|                             | There are      | 4     | 36.4| 7     | 63.6| 11    | 100.0 | (1.385–18.896) |
|                             | Total          | 80    | 70.8| 33    | 29.2| 113   | 100.0 |

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ², 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
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.
### Table 8. Blood groups, risk factors, and lethal hydrocephalus.

| Indicators | Groups               | Another group | A+   | Total | \( \chi^2 \) | \( P \)  | OR             |
|------------|----------------------|---------------|------|-------|----------------|--------|-----------------|
|            | N   | %     | N    | %     | N    | %     |               |        |
| Consanguinity | No       | 63 | 81.8 | 14 | 18.2 | 77 | 100.0 | 4.206 | 0.04 | 3.375 |
|            | 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 | \( \chi^2 \) | \( P \)  | OR             |
|------------|----------------------|---------------|------|-------|----------------|--------|-----------------|
|            | N   | %     | N    | %     | N    | %     |               |        |
| Miscarriage | No       | 74 | 74.0 | 26 | 26.0 | 100 |          | 4.315 | 0.038 | 3.321 |
|            | There are | 6  | 46.2 | 7  | 53.8 | 13  |          | (1.022–10.789) |       |       |
|            | Total    | 80 | 70.8 | 33 | 29.2 | 113 |          |               |       |       |

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

| Indicators | Groups               | Without polygyria | Polygyria | Total | \( \chi^2 \) | \( P \)  | OR             |
|------------|----------------------|-------------------|-----------|-------|----------------|--------|-----------------|
|            | N   | %     | N    | %     | N    | %     |               |        |
| Maternal age | ≤35      | 82 | 92.1 | 7  | 7.9  | 89 | 100.0 | 4.894 | 0.027 | 4.894 |
|            | ≥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 | \( \chi^2 \) | \( P \)  | OR             |
|------------|----------------------|----------------------------------------|-------------------------------|-------|----------------|--------|-----------------|
|            | N   | %     | N    | %     | N    | %     |               |        |
| Abortion   | No       | 83 | 86.5 | 13 | 13.5 | 96 | 100.0 | 4.886 | 0.027 | 3.483 |
|            | There are | 11 | 64.7 | 6  | 35.3 | 17 | 100.0 | (1.099–1.040) |       |       |
|            | 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 |
|            | There are | 22 | 71.0 | 9  | 29.0 | 31 | 100.0 | (1.048–8.052) |       |       |
|            | 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 |
|            | There are | 19 | 73.1 | 7  | 26.9 | 26 | 100.0 | (0.977–12.274) |       |       |
|            | 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 |
|            | There are | 16 | 69.6 | 7  | 30.4 | 23 | 100.0 | (0.969–8.342) |       |       |
|            | Total    | 94 | 83.2 | 19 | 16.8 | 113 | 100.0 |               |       |       |

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; \( \chi^2 \), chi-square; \( P \), sig.
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 gyrification, 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 patho-genetic 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.

Author details

Tanya Kitova¹*, Borislav Kitov², Denis Milkov⁴ and Aida Masmoudi³

*Address all correspondence to: tanyakitova@yahoo.com

1 Department of Anatomy, Histology and Embryology, Medical University of Plovdiv, Plovdiv, Bulgaria

2 Department of Neurosurgery, Medical University of Plovdiv, Plovdiv, Bulgaria

3 University of Tunis—El Manar, Faculty of Medicine of Tunis, Center of Maternity and Neonatology of Tunis, Tunis, Tunisia

4 Medical Faculty, Medical University of Plovdiv, Plovdiv, Bulgaria

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