

# CEPHALIC DYSRAPHISMS - ENCEPHALOCELE AND EXENCEPHALY

Tanya Kitova<sup>1</sup>, Kristina Kilova<sup>2</sup>, Denis Milkov<sup>2</sup>, Victor Marchev<sup>2</sup>, Daniel Vassilev<sup>2</sup>, Soumeya Siala Gaigi<sup>3</sup>

<sup>1</sup>*Department of Anatomy, Histology and Embryology, Medical University of Plovdiv*

<sup>2</sup>*Medical University of Plovdiv*

<sup>3</sup>*Clinic of Fetopathology, Center of Maternity and Neonatology, Tunis*

## ABSTRACT

Encephalocele and exencephaly are congenital malformations of the central nervous system with a frequency in Europe of 2.3/1000 births for the period 2003-2007.

**PURPOSE:** To examine the macroscopic and microscopic characteristics of the malformations encephalocele and exencephaly and the associated abnormalities of the internal organs in autopsies of fetuses with neural tube defects (NTD).

**MATERIALS AND METHODS:** Twenty-four fetuses with encephalocele and exencephaly were examined during a period of three years (2006-2009) in the Clinic of Fetopathology at the Center for Maternity and Neonatology – Tunisia. The fetuses were the result of interrupted pregnancies due to medical reasons, intra-uterine fetal death, spontaneous abortions and neonatal death.

**RESULTS:** The most common encephalocele was the occipital – 25.0%, followed by the parietal – 4.17%. Exencephaly was found in 12.50% of the studied cases. Associated gastrointestinal anomalies are anomalies of the mesentery, hepatosplenomegaly, polysplenia, a supplemental spleen, and hepatomegaly. Associated anomalies of the urinary system are tubular bladder, polycystic kidney and abnormalities in the shape and position of the kidney. The respiratory system anomalies are represented by hypoplasia, improper lung lobulation, and situs inversus. The anomalies of the abdominal wall were severe: agenesis of the diaphragmal dome and agenesis of the umbilical artery (4.2%, 8.3%). The genetic study found a karyotype of triploidy (69, XXX) for 4.2% of the fetuses.

**CONCLUSION:** The sonographic examination should be a careful inspection of all systems and organs of the fetus and the amniotic fluid. In complicated cases of fetuses with encephalocele and exencephaly genetic counseling is imperative.

**Key words:** *encephalocele, exencephaly, associated anomalies, triploidy, hypoplasia, prenatal diagnosis*

---

### Address for correspondence:

Tanya Kitova

Department of Anatomy, Histology and Embryology

Medical University of Plovdiv

Bul. V. Aprilov 15A

Plovdiv 4003

Phone: 0887855857

e-mail: tanyakitova@yahoo.com

**Received:** January 30, 2013

**Accepted:** February 11, 2013

## INTRODUCTION

Encephalocele and exencephaly are congenital neural tube defects (NTDs). The frequency of this group of malformations in Europe was 2.3 per 1000 births for the period 2003-2007, in some countries, however, a higher incidence was found (1). For example, according to Dogan H et al. (2) and Onrat ST et al. (3) the average frequency of NTDs in

Turkey is approximately 4/1000, and the incidence of encephalocele is 0.23%. The highest incidence of encephalocele was found to be in China – 14.7 per 10 000 births (4). Recent studies have found that folic acid supplementation in the periconception period is particularly important. For example, after the introduction of mandatory folic acid supplementation in the U.S. for the period 1996-2006, a reduction of encephalocele by 34% was found when compared to the period 1980-1992 (5).

Data for Bulgaria is scarce. According to data of the National Statistics Institute for the year 2010, the stillbirths caused by congenital malformations and chromosomal aberrations were 83 or at a rate of 1.10 per 1000 live births. According to Kovacheva K, neural tube defects during the period 1998-2006 in the Pleven region were at a rate of 2 per 10,000 births (6).

**Embryology:** The closure of the neural tube is a complex morphogenetic process that begins with the lifting of the edges of the nerve groove between the 22<sup>nd</sup> and 24<sup>th</sup> day of the embryonic development. The process continues with apposition and fusion of the nerve edges, a median convergent extension and gradual separation of the neuroepithelium. On the twenty-third day two neuroporus can be distinguished. Between the 24<sup>th</sup> and 26<sup>th</sup> day the rostral neuroporus closes, while the caudal neuroporus closes by the 25<sup>th</sup> to 28<sup>th</sup> day. This interrupts the communication with the amniotic cavity (7).

Due to the importance of the problem of congenital malformations in fetal medicine, our goal is to characterize macro- and microscopically encephalocele and exencephaly and their associated anomalies of the internal organs in autopsies of fetuses with these malformations.

## MATERIALS AND METHODS

Twenty-four fetuses with encephalocele and exencephaly were examined from a total of 150 fetuses with NTD which were diagnosed during a period of three years (01.2006-01.2009) in the Clinic of Fetopathology at the Center for Maternity and Neonatology – Tunis, Tunisia.

The fetuses have been the result of pregnancies interrupted due to medical reasons, intrauterine fetal death, spontaneous abortions and neonatal death. The full range of data available for each

case (fetus) has been compiled in a personal file which includes: photographic documentation, x-rays, karyotype, fetal biometry, and documentary information from the autopsy of fetuses obtained from the visual inspection and the internal macroscopic examination of the cavities and of the internal organs, situs thoracis, situs abdominis, the pelvic cavity, and the retroperitoneal compartment. All examination was performed after authorization for autopsy, genetic testing and biopsy specimen collection. The cranial cavity and the brain were examined after fixation with formalin (an aqueous solution of 40% formaldehyde) for a period of one to six months. Each fetus's organs were weighed and fragments were taken for histological examination of the system from different parts of the brain. The results of the autopsy were added to the files in three stages: the first stage - from the macroscopic autopsy, the second - from the microscopic results of biopsy fragments and the third stage – from the macro and microscopic brain examination.

The data has been statistically processed by the statistical program SPSS-V17.

## RESULTS

### *Maternal characteristics:*

- ❖ The average age was 31.5 years.
- ❖ The average number of pregnancies was  $2.14 \pm 0.457$  with a range from one to ten pregnancies.
- ❖ The average number of births was  $0.96 \pm 0.185$  with a range from zero to three births.
- ❖ Blood type: type B+ in 40.0% of examined fetuses, type O in 35.0% of them
- ❖ Diabetes and toxoplasmosis – 12.5%
- ❖ Miscarriages – 8.3%
- ❖ Consanguinity – 33.3% of the fetuses are from consanguineous marriages. Of these, 8.3% are of first degree and 8.3% of second degree.

### *Characteristics of fetuses:*

- ❖ Gender – an equal distribution of the anomalies between the two genders
- ❖ Average age – 20 gestation weeks.
- ❖ Average weight – 398.8 grams

- ❖ Genetic examination: Genetic testing found a karyotype of triploidy (69, XXX) in 4.2% of the fetuses with cephalic dysraphisms.

#### *Macroscopic examination of the dysraphism:*

Twenty-one fetuses were found to have a herniation of the brain that leaves the cranial cavity through a rounded bone defect. The hernial sac is formed from the meninges and the contents of different encephalic fragments. These 21 cases were diagnosed as encephalocele – two frontal, one parietal and six occipital (Figure 1). In twelve of the fetuses the location was not specified (Table 1). In three fetuses, the prolapse through the bone defect



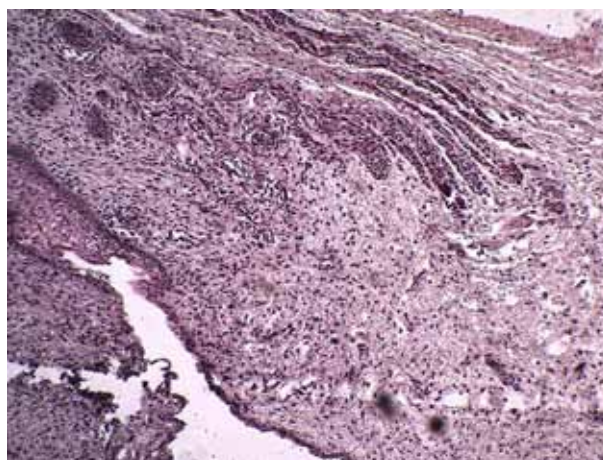
*Fig. 1. This fetus has frontal encephalocele (12 cm in diameter), a weight of 830 grams, and is in the 26th week of gestation*

was significant and the brain was outside the cranial cavity. These cases were diagnosed as a major form of encephalocele – exencephaly.

#### *Microscopic examination of the dysraphism:*

The microscopic study indicates herniated brain tissue, which is disorganized with an expressed glio-neuronal proliferation, heterotopias, and polymicrogyria (Figure 2).

#### *Anomalies of the internal organs and the abdominal wall:*



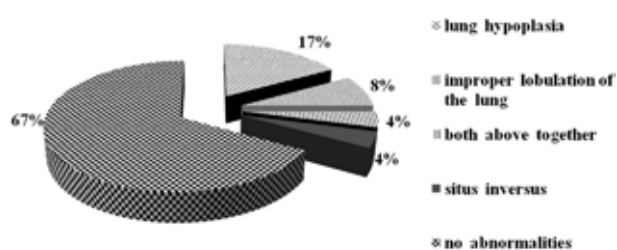
*Fig. 2. Occipital encephalocele. Heterotopias*

The agenesis of one of the diaphragmal domes and the agenesis of one a. umbilicalis (4.2%, 8.3%) were the identified anomalies of the **abdominal wall** which are associated with encephalocele and exencephaly. Abnormalities of the **respiratory system** (Figure 3) in fetuses with a dysraphism of the cephalic pole - encephalocele and exencephaly are hypoplasia of the lungs (diagnosed by size and weight), incorrect lobulation, and situs inversus (by the hilus elements, lobes and fissures of the lungs). Lung hypoplasia was found in 17% of the cases, incorrect lobulation in 8%, and the combination of both and situs inversus represent 4% of the cases each. Abnormalities of the **digestive system** (Figure 4), which are associated with encephalocele and exencephaly in almost a third of the fetal anomalies (30%), were those of the mesentery. In those cases, the mesentery was not morphologically distinct. Twelve percent of the anomalies were in the parenchymal organs - hepatosplenomegaly, polysplenia, supplemental spleen and hepatomegaly. Over half

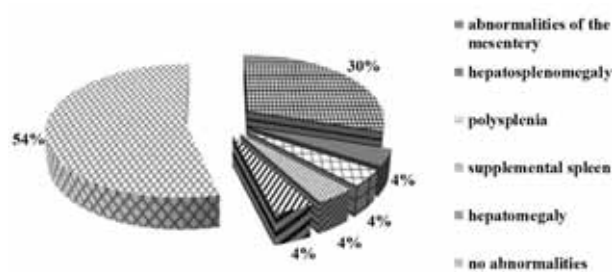
*Tabl 1. Distribution of the anomalies with regards to localization*

**Abbreviations:** Encephalocele - ECC

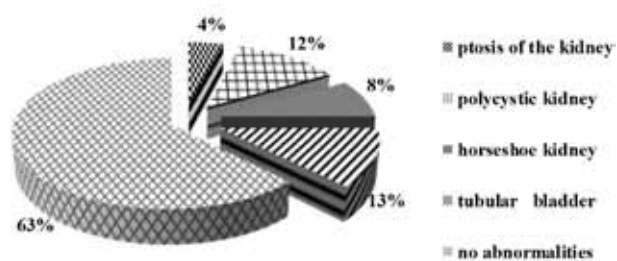
Diagnosis	Number of cases	%	Mean error
Encephalocele ECC	12	50,00%	-
Exencephaly	3	12,50%	6,75%
<b>ECC occipitale</b>	6	25,00%	8,84%
ECC parietale	1	4,17%	4,08%
<b>ECC frontalis</b>	2	<b>8,33%</b>	<b>5,64%</b>
Total	24	100,00%	-



*Fig. 3. Associated abnormalities of the respiratory system*



*Fig. 4. Associated abnormalities of digestive system*



*Fig. 5. Associated abnormalities of the urinary system*

(54%) of the examined fetuses did not have digestive system abnormalities. Studies of the **urinary system** (Figure 5) show that, over 60% of the fetuses

with encephalocele and exencephaly did not have associated anomalies of this system. The remaining 40 percent, however, had anomalies such as tubular bladder, polycystic kidney and abnormalities in the shape and position of the kidney. Each of these abnormalities was observed for 13%, 12%, 8%, and 4% of the fetuses, respectively. Abnormalities of the **reproductive, endocrine and cardiovascular systems** were not found.

## DISCUSSION

The analysis of epidemiological indicators shows that the age and blood group of the mother are not risk factors for fetuses with these malformations (8). Both genders were equally affected in both of the studied malformations which can be developed in fetuses from consanguineous marriages, as well as in fetuses from non-consanguineous marriages.

The most common location of encephalocele in this study was the occipital – 25.0 percent. The occipital localization is the most common in the European continent with a frequency of 1/5000. In Asia and Africa, however, more common are the nasal and fronto-parietal localizations. An explanation for this difference can be sought in the multifactorial genesis of malformations (9,10). Encephalocele and exencephaly are two degrees of the same malformation affecting the soft tissue, the skull, the meninges and the brain simultaneously. They represent a defect in the closure of the neural tube. The development of the nervous system is a result of a cumulative process of interaction between the genetic information and environmental factors (11,12). Uneven closure of the neural tube and in particular neuroporus anterior (24-26 days of embryonic development) increases the contact with the amniotic fluid abnormally and leads to neuroepithelial degeneration with a loss of neural tissue by the end of the pregnancy. The microscopic findings of the present study confirm this.

Encephalocele and exencephaly can occur in children with a normal karyotype but can also be a consequence of chromosomal aberration (13). This study proves encephalocele in cases of triploidy; so far about 200 genes associated with neural tube defects have been described (14). Triploidy could also be associated with other anomalies (15). Encephalocele and exencephaly have different associated anomalies of the internal organs and the central nervous system

(16). In 46% of fetuses with encephalocele and exencephaly associated anomalies of the digestive system were found, and amongst them those of the mesentery are the most common. Mesenteric abnormalities are the result of an incomplete 180° rotation in the middle part of the primary intestine during the period from seventh to eleventh week of gestation. Abnormalities such as polysplenia can be the result of a disorder in condensation of the fetal mesenchyme in mesogastrium posterior and abnormal lateralization during the same period (17). Associated anomalies of the respiratory system in fetuses with encephalocele and exencephaly were 43% where hypoplasia of the lungs represents the largest share. Hypoplasia is closely related to deviations in the amount of amniotic fluid and in particular oligoamnios (18).

Associated anomalies of the urinary system are present in 37% of the cases. Hypoplasia of the bladder (tubular bladder), ectopia and anomalies in the shape and size of the kidneys often lead to secondary development of Potter's syndrome (19).

Anomalies of the abdominal wall may be a part of the associated anomalies of the internal organs, and should be actively sought in cases of encephalocele and exencephaly (20). The most commonly associated anomalies in the present study are anomalies of the digestive, urinary and respiratory systems. Anomalies of the abdominal wall are rare but severe: agenesis of the diaphragmal dome and umbilical artery agenesis.

## CONCLUSION

The search for encephalocele and exencephaly in the clinic during the twelfth, sixteenth and twenty-second weeks of gestation should be performed with great scrutiny. Great importance must be placed on the search for any anomalies in the systems and organs of the fetus as well as anomalies of the amniotic fluid during the examination. In complicated cases of fetuses with both encephalocele and exencephaly, genetic counseling is necessary.

## REFERENCES

1. Dolk, H., M. Loane, E. Garne. The prevalence of congenital anomalies in Europe.- *Adv. Exp. Med. Biol.*, **686**, 2010, 349-364.
2. Doğan, H., S. Sahinoglu. Fetuses with neural tube defects: ethical approaches and the role of health care professionals in Turkish health care institutions.- *Nurs. Ethics*, **12**(1), 2005, 59-78.
3. Onrat, S. T., H. Seyman, M. Konuk. Incidence of neural tube defects in Afyonkarahisar, Western Turkey.- *Genet. Mol. Res.*, **8**, 2009, No 1, 154-161.
4. Li, Z., A. Ren, L. Zhang, R. Ye, S. Li, J. Zheng et al. Extremely high prevalence of neural tube defects in a 4-county area in Shanxi Province, China.- *Birth Defects Res. A Clin. Mol. Teratol.*, **76**, 2006, No 4, 237-240.
5. Bower, C., H. D'Antoine, F. J. Stanley. Neural tube defects in Australia: trends in encephaloceles and other neural tube defects before and after promotion of folic acid supplementation and voluntary food fortification.- *Birth Defects Res. A Clin. Mol. Teratol.*, **85**, 2009, No 4, 269-273.
6. Kovacheva, K., M. Simeonova, M. Ionov, R. Rosmanova. Congenital anomalies among live-birth infants and their place in the structure of neonatal mortality--the Higher Medical Institute, Pleven (1993-97).- *Akush. Ginekol. (Sofia)*, **39**, 2000, No 2, 20-23.
7. Carmine, D., A. B. Clemente. Gray's Anatomy. Thirtieth American Edition, 1984, 34-39, 123-126.
8. Stoll, C., B. Dott, Y. Roth, Y. Alembik. Etiologic and epidemiologic aspects of neural tube defects.- *Arch. Fr. Pediatr.*, **45**, 1988, No 9, 617-622.
9. Onuigbo, W. Encephaloceles in Nigerian Igbos.- *J. Neurol. Neurosurg. Psychiatry*, **40**, 1977, No 7, 726.
10. Ambe, J. P., A. G. Madziga, G. O. Akpede, Y. Mava. Pattern and outcome of congenital malformations in newborn babies in a Nigerian teaching hospital.- *West Afr. J. Med.*, **29**, 2010, No 1, 24-29.
11. Bachraoui, A. Le syndrome de Meckel. Diagnostic foetopathologique et prenatal. Consideration générales, Apropos de 9 cas. Thèse de doctorat en médecine Tunis, 1999.
12. Carles, D., F. Serville, E. Alberti, W. Weichhold. Analysis of 1410 examinations of fetal pathology at the University Hospitals of Bordeaux.- *J. Gynecol. Obstet. Biol. Reprod. (Paris)*, **20**, 1991, No 4, 577-586.
13. Etheredge, A. J., R. H. Finnell, S. L. Carmichael, E. J. Lammer, H. Zhu, L. E. Mitchell, G. M. Shaw. Maternal and infant gene-folate interactions and the risk of neural tube defects.- *Am. J. Med. Genet. A.*, **158A**, 2012, No 10, 2439-2446.
14. Greene, N. D., P. Stanier, M. Copp. Genetics of human neural tube defects.- *Hum. Mol. Genet.*, **18**, 2009, No R2, 113-129.

15. Sergi, C., M. Schiesser, S. Adam, H. F. Otto. Analysis of the spectrum of malformations in human fetuses of the second and third trimester of pregnancy with human triploidy.- *Pathologica*, **92**, 2000, No 4, 257-263.
16. Stoll, C., Y. Alembik, B. Dott. Associated malformations in cases with neural tube defects.- *Genet. Couns.*, **18**, 2007, No 2, 209-215.
17. Gilbert-Barnes, E., D. Debich-Spicer, M. M. Cohen Jr, J. M. Opitz. Evidence for the „midline“ hypothesis in associated defects of laterality formation and multiple midline anomalies.- *Am. J. Med. Genet.*, **101**, 2001, No 4, 382-387.
18. Laudy, J. A., J. W. Wladimiroff. The fetal lung. 2: Pulmonary hypoplasia.- *Ultrasound Obstet. Gynecol.*, **16**, 2000, No 5, 482-494.
19. Rachdi, R., M. Kaabi, H. M'Hamdi, I. Chtioui, M. Chibani, S. Gaigi. Potter's reno-facial syndrome.- *Tunis. Med.*, **82**, 2004, No 7, 690-697.
20. Froster-Iskenius, U., P. Meinecke. Encephalocele, radial defects, cardiac, gastrointestinal, anal, and renal anomalies: a new multiple congenital anomaly (MCA) syndrome?- *Clin. Dysmorphol.*, **1**, 1992, No 1, 37-41.