

CLINICAL CASE

ANENCEPHALY CAUSED BY FOLATE DEFICIENCY - TWO CASE REPORTS AND REVIEW OF THE LITERATURE**Liana Pleș^{1,2}, Romina-Marina Sima^{1,2}, Delia Carp¹, M. O. Poenaru^{1,2}, O. G. Olaru^{1,2} Anca-Daniela Stănescu^{1,2}**¹„St. John” Hospital, „Bucur” Maternity, Bucharest, Romania² The University of Medicine and Pharmacy „Carol Davila”, Bucharest, Romania

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Abstract

Anencephaly represents a severe defect of development of the neuraxis, in which the developing forebrain and variable amounts of the brainstem are exposed in utero and fail to develop or are destroyed. Patient SM, 27 years of age, referred to our clinic for obstetrical ultrasound. The patient had no previous ultrasound examination in the current pregnancy. At the presentation time, the pregnancy age established by ultrasound was of 13 weeks of gestation. The fetal medicine specialist concluded that the fetus had anencephaly. The couple decided the termination of pregnancy. Patient PC came to our hospital for prenatal care. The first ultrasound examination was performed at 10 weeks of pregnancy. The fetal-medicine specialist identified the same severe cranial malformation as in the previous case: anencephaly. The peculiarity of this case was the early ultrasound diagnosis. The question that arises from the two situations is: why anencephaly? The answer for both cases may be: folate deficiency. Both mothers didn't receive any folate supplement before conception or during pregnancy. Ultrasound is the gold standard for anencephaly diagnosis. Prenatal detection was followed by termination of the pregnancy. The main cause of anencephaly could be folate deficiency for both cases.

Keywords: *ultrasound, termination of pregnancy, cranial malformations***Introduction**

The mechanisms of craniofacial abnormalities resulting in anencephaly can be abnormal neural induction from prosencephalic and mesencephalic neural crest tissue [1]. Anencephaly represents a severe defect of development of the neuraxis, in which the developing forebrain and variable amounts of the brainstem are exposed in utero and fail to develop or are destroyed [2]. Experimental and observational studies proved that in early brain development an important role belongs to the folic acid. In pregnancy, there is an active

placental transfer of folate and the fetal brain has higher levels of B9 than in adults [3].

Case presentation**Case 1**

Patient SM, 27 years of age, referred to our clinic for obstetrical ultrasound. She had no previous ultrasound examination in the current pregnancy. The patient didn't follow our national program of prenatal care. She had no present medical, surgical or obstetrical history

(pregnancy or abortion before). At the presentation time it was diagnosed by ultrasound a pregnancy of 13 weeks of gestation. The first ultrasound specialist observed that the fetus had abnormal cephalic appearance and referred the case to the fetal medicine specialist who confirmed the diagnosis of anencephaly (Figures 1 and 2). The couple received the optimal explanations concerning the evolution and outcome of the fetus affected by that severe congenital malformation. They decided the termination of pregnancy because of that life threatening fetal malformation. The pregnancy termination was accomplished at 14 weeks of gestation by D&C. The maternal outcome was favorable. Based on financial considerations the couple declined the genetic diagnosis of the fetus. The question raised by the couple was about the cause of anencephaly? The answer for this case could be: folate deficiency. The mother didn't receive any folate supplement before or during pregnancy.



Figure 1 - 3D Ultrasound examination of the anencephalic fetus



Figure 2 - The absence of the brain and calvaria on coronal view of the fetal head

Case 2

Patient PC was referred to our hospital for prenatal care. At the first clinical examination she declared 10 weeks of amenorrhea. The patient was 30 years old secundipara without any medical history. Regarding the obstetrical history she had a previous spontaneous abortion at 7 weeks of pregnancy. The cause of abortion is unknown and considering that it was the first miscarriage no genetic examination was indicated.



Figure 3 - 3D Ultrasound examination of the anencephalic fetus at 10 weeks of pregnancy



Figure 4 - 2D Sagittal section of anencephalic fetus at 10 weeks of pregnancy

In the current pregnancy the patient was first examined by the general physician and the biological findings were normal (blood count sample, kidney, liver evaluation were normal). The first ultrasound examination was performed at 10 weeks of pregnancy. The fetal-medicine specialist identified the same severe cranial malformation as the previous case: anencephaly (Figures 3 and 4). The peculiarity of this case was the early ultrasound diagnosis. The couple decided in favor of pregnancy termination. The common point of the two cases is the folate deficiency. None of the two patients received folate supplement for pregnancy. This can justify the anencephaly occurrence.

Discussions

Neural tube defects (NTDs) are severe birth defects, in which the neural tube fails to close completely. They occur early in embryogenesis, being the result of an aberrant expression of an undefined developmental gene or family of genes. The nervous system develops in a precise temporal embryologic sequence and an interruption in a developmental sequence will alter the remaining development [4]. The anterior and posterior neuropores close last, which indicates that they are the most vulnerable to defects [5,6].

NTDs can be classified, based on the presence or absence of exposed neural tissue, as open or closed types. Open NTDs, due to failure of primary neurulation, involve the entire central nervous system [7]. Closed NTDs result from a defect in secondary neurulation and involve only the spine. The neural tissue is not exposed, and the defect is fully epithelialized by normal or dysplastic skin [8]. Cranial abnormalities include: anencephaly, encephalocele (meningocele or meningomyelocele), craniorachischisis totalis and congenital dermal sinus. Spinal presentations include: spina bifida aperta (cystica), myelomeningocele, meningocele, myeloschisis, congenital dermal sinus, lipomatous malformations (lipomyelomeningoceles), split-cord malformations, diastematomyelia, diplomyelia, caudal agenesis [9].

The prevalence of anencephaly in the United States in 2001 was 9.40 per 100,000 live births [10]. It is reported that birth prevalence of anencephaly decreased 20 percent between the 1999 to 2000 period and the 2003 to 2004 survey periods [11]. This decline is based on mandatory fortification of foods with folic acid, which began in January 1998. In Europe the prevalence of anencephaly is higher in Ireland and the British Islands as compared with continental Europe [12]. In a registry of 456 affected stillborn and liveborn infants in British Columbia, additional malformations that accompanied anencephaly were cleft lip and/or palate or omphalocele, in 12.7 percent [13]. There were also founded craniofacial and ocular anomalies and in some case cardiac, pulmonary, renal, aganglionosis of the intestine and skeletal malformations [14].

Folic acid, known as vitamin B9 or folate, belongs to the B group of vitamins. It is a water soluble vitamin. The body cannot store vitamin B9 and needs a supply of 200-400 µg/day. In pregnancy, the requirement increases to 500-800 µg/day.

Folate is usually found in foods like: liver, chicken, kidney, dried beans, soya products, nuts and almonds, potatoes, spinach, broccoli, bananas, oranges, peaches [15].

WHO developed the evidence-based folate concentration guidelines using the WHO Handbook for Guideline Development. WHO recommendations are:

At the population level, RBC folate concentrations should be >400 ng/mL (906 nmol/L) in women of reproductive age to achieve the greatest reduction of NTDs (strong recommendation, low-quality evidence).

The RBC folate threshold of >400 ng/mL (906 nmol/L) can be used as an indicator of folate insufficiency in women of reproductive age (strong recommendation, low-quality evidence). Because low folate concentrations cannot explain all cases of NTDs, this threshold cannot predict the individual risk for having a NTD-affected pregnancy and thus is only useful at the population level.

No serum folate threshold is recommended for prevention of NTDs in women of reproductive age at the population level (strong recommendation, low-quality evidence). Countries interested in using this

indicator might consider first establishing the relationship between both serum and RBC folate concentrations and use the threshold value for RBC folate concentration to establish the corresponding threshold in serum.

Microbiological assay is recommended as the most reliable choice to obtain comparable results for RBC folate concentration across countries (strong recommendation, moderate-quality evidence) [16].

The production of nucleic acid, an essential component of DNA and RNA, is based on the availability of folic acid [17]. Randomized controlled trials and observational studies have shown that daily intake of folate, periconceptional and during pregnancy, considerably reduces the risk for NTDs [18]. The recommended intakes are 4 mg/d for those at high risk and 0.4 mg/d for all others [19].

Conclusions

We presented two cases of early prenatal diagnosis of anencephaly. Ultrasound is the gold standard of diagnosis. Prenatal detection was followed by termination of the pregnancy. The main cause of anencephaly was folate deficiency for both cases.

References

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