MEDICUS

ISSN 1409-6366 UDC 61 Vol · 31 (1) · 2026

Original scientific paper

Profesional paper

Review

Case report

FETAL MALFORMATIONS - ANENCEPHALY AND SPINA BIFIDA, AS AN INDICATION FOR PREGNANCY TERMINATION IN THE SECOND TRIMESTER

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Medicus 2026, Vol. 31 (1): 92-95

ABSTRACT

Introduction: Anencephaly is the most severe malformation of the central nervous system. It is common type of neural tube defect and is characterized by the complete or partial absence of the calvaria and brain. It is a fatal disease and newborns born with this anomaly usually live less than a day. It's incidence is 1-5/1000 births. The occurrence of neural tube defects is due to a combination of genetic and environmental factors.

Case report: A 31-year-old patient with a third pregnancy., at 15+4 weeks of gestation. She reported smoking 20 cigarettes per day and taking folic acid supplements starting at 6 gestational weeks. On ultrasound examination, there was a fetus with a positive cardiac action, abdominal circumference and femur length corresponding to 15 weeks of gestation. Biparietal diameter and head circumference could not be measured due to protrusion of brain tissue through a calvarial defect. We performed labor induction with oxytocin and after expulsion of the fetus and placenta, an instrumental revision of the uterine cavity was performed under general anesthesia. According to the autopsy report, the fetus had low-set auricles, a stocky neck, protrusion of the eyeballs and a frog-like appearance. External inspection showed a congenital malformation of the central nervous system represented by the absence of the bones of calvaria and absence of brain tissue with the presence of an area cerebrovasculosa measuring 2x1.7 cm and a cleft of the vertebral arches in the lumbar region measuring 0.5cm covered with skin and soft tissues (spina bifida occulta).

Conclusion: The simplest way to reduce the incidence of neural tube defects is to advise women of reproductive age to take folic acid supplements. Fetal ultrasonography is the gold standard for detecting neural tube defects. Anencephaly should be detected as early as possible, in order to perform a timely termination of pregnancy.

Key words: anencephaly, neural tube defects, folic acid suplementation, ultrasound

INTRODUCTION

Anencephaly is the most severe malformation of the central nervous system. It is common type of neural tube defect and is characterized by the complete or partial absence of the calvaria and absent brain. The brainstem, diencephalon and cerebellum are commonly present [1]. As the central nervous system develops in embrio, the neural plate folds and fuses, forming the neural tube. Any disruption of the neural tube closure process can result in structural abnormalities that are called neural tube defects. Anencephaly results from the failure of the neural tube to close at its rostral end during

fetal development [2]. It is a fatal disease and newborns born with this anomaly usually live less than a day. It's incidence is 1-5 per 1000 births [3]. The other neural tube defect is spina bifida caused by failure of closure of the caudal (spinal) part of the neural tube in the 4th week of gestation [4]. Spina bifida has two forms: occulta and aperta. Spina bifida occulta is a closed form where the lesion is covered with skin and the spinal cord is not exposed [5]. In the cases of spina bifida aperta, the spinal cord is exposed to the surrounding environment, without skin covering [4,6]. Severity ranges from asymptomatic spina bifida occulta to severe forms - spina bifida aperta (meningomyelocele), with spinal cord exposure and neurological dysfunctions: mobility problems, bowel and bladder dysfunction, hydrocephalus [7]

The occurrence of neural tube defects is due to a combination of genetic and environmental factors [8] After the birth of one child with this malformation, there is a 4% risk that a subsequent child will be affected [9]. Insufficient intake of folic acid in the diet (or as a supplement) before and during the first trimester of pregnancy plays an important role [8]. Other risk factors are: some epilepsy medications (valproic acid, phenytoin, carbamazepin), obesity and poorly controlled diabetes. [9]. Some studies suggest that neural tube defects and spontaneous abortions are more common in pregnant women who experience high temperatures (hot tub, sauna, having a fever) during the first 4-6 gestational weeks [8,10].

CASE REPORT

We present a case of a 31-year-old female patient with a third pregnancy, who was referred to our hospital for an ultrasound examination at 15+4 weeks of gestation. The previous two pregnancies were normal, ending with spontaneous delivery. In this pregnancy, she reported smoking 20 cigarettes per day and receiving folic acid suplementation starting at 6 weeks of gestation. The history of past illnesses and allergies was negative. PRISCA 1 was not performed, and microbiological tests were negative. On ultrasound examination, a fetus with a positive cardiac action was detected, with abdominal circumference and femur length corresponding to 15 weeks of gestation, but biparietal diameter and head circumference could not be measured due to protrusion of brain tissue through a calvarial defect [Figure 1]. The patient was hospitalized with suspicion of encephalocele. With the patient's prior consent, we performed labor induction with oxytocin and after expulsion of the fetus and placenta, an instrumental revision of the uterine cavity was performed under general intravenous anesthesia. Anesthesia and intervention underwere without complications. Uterotonic and antibiotic therapy were administered.

We submited the fetus and placenta to autopsy and histopathological analysis, with the following findings: a female fetus with a body weight of 51 grams and a body length of 11 cm. The fetus had low-set auricles, a stocky neck, protrusion of the eyeballs and a frog-like appearance. External inspection showed a congenital malformation of the central nervous system represented by the absence of the bones of the calvaria and the absence of brain tissue with the presence of an area cerebrovasculosa measuring 2x1.7 cm and a cleft of the vertebral arches in the lumbar region measuring 0.5 cm covered with skin and soft tissues, which was consistent with spina bifida occulta. After opening the chest and abdominal cavity, the visceral organs were neatly placed in the appropriate anatomical positions, properly formed without the presence of developmental malformations. A placenta measuring 8x4x3 cm and weighing 70 g had a regular structure. The amniotic membranes were smooth and shiny. The umbilical cord was paracentrally inserted, 12 cm long, and 3 blood vessels were visible on the cross-section. Microscopically, the cross-sections of the area cerebrovasculosa showed remnants of primitive neural tissue surrounded by edematous connective tissue with embedded proliferated blood vessels. The lungs had fetal atelectasis, and the remaining visceral organs were immature, appropriate for gestational age. Placental samples showed regular placental tissue and amniotic membranes without pathological substrate.

Figure 1. Ultrasonography that shows the apsance of brain hemisferes, normal lateral ventricles

Figure 2. The aborted fetus with a large cranial defect

DISCUSSION

Anencephaly is one of the most common anomalies resulting from a defect in the development of the neural tube and there is an absent part of the calvaria or the entire calvaria, with an absent brain. The incidence is 1-5/1000 births and mortality is 100%, intrauterine or in the first hours after birth. The cause of this malformation is unknown, but there are several risk factors such as genetic mutations and polymorphisms of certain genes, maternal diabetes, obesity, exposure to certain drugs or toxins, as well as a positive family history of neural tube defects (for example, a previous pregnancy with a fetus with anencephaly or spina bifida). The most important nutritional risk factor is folic acid deficiency, due to insufficient intake or due to polymorphisms of the gene encoding the enzyme involved in folic acid metabolism (methyltetrahydrofolate reductase - MTHFR). Some polymorphisms of this gene cause thermolability of the enzyme and its reduced enzymatic activity and these individuals need to have higher levels of folic acid in plasma to meet their needs (higher intake through food or supplements) [11].

The diagnosis of this condition is made by ultrasonography. The presence of anencephaly can be detected even in the first trimester. An important factor for an accurate ultrasound diagnosis of is gestational age. Calcification of the skull is complete by 10 weeks of gestation, and the diagnosis may be missed if the ultrasound examination is performed at a gestational age of less than 11 weeks. In ultrasound imaging, there is an absence of the upper part of the cranium and absence of brain tissue in place of the cerebral hemispheres [12]. Also, in ~ 90 % of cases of anencephaly, serum alpha-fetoprotein levels are increaed in maternal blood and also in the amniotic fluid [13].

In the second trimester of pregnancy, the “frog eyes” sign is detected by ultrasound due to the absence of the brain above the orbits. In 30-50% of cases of anencephaly, polyhydramnion is also present, due to intraamniotic leakage of cerebrospinal fluid, impaired fetal swallowing and increased urine production due to a lack of antidiuretic hormone.

Anencephaly is a lethal anomaly, so ultrasound diagnosis is essential to perform timely termination of pregnancy. Prevention of neural tube defects is also important, and most American, British and Canadian organizations recommend taking 0.4-0.8 mg/day of folic acid, and if the woman has had a previous pregnancy with this type of anomaly, the recommended dose is 4 mg/day [14].

According to the recommendations of the World Health Organization, it is necessary to take 0.4 mg of folic acid daily as a supplement to prevent the occurrence of neural tube defects, preferably one month before conception and during the first three months of pregnancy. If folic acid supplementation is started after the first trimester, it will not be effective, because the neural tube has already been formed [15]. In our case, the patient suplemented 0.4 mg of folic acid daily starting from the sixth week of gestation, which was probably late, because the critical period for the development of anencephaly and spina bifida is earlier, in the fourth week of gestation. Women with polymorphisms of genes encoding enzymes involved in folate metabolism have higher folic acid needs than other women. By enriching food with folic acid, optimal levels of folic acid in plasma cannot be achieved. Therefore, supplementation in the preconception period and in the first trimester of pregnancy is the best way to improve folic acid levels [16]. Because of the high prevalence of MTHFR genetic polymorphisms in the general population, there is a concern about reduced enzymatic activity. Newer research has focused on supplementation with L-methylfolate, as a biologicaly active form, rather than folic acid [18].

The other problem is that ~50% of pregnancies are unplanned. If women has unplanned pregnancy and not used supplements, this preventive method is inefective. At the time of the absence of menstrual cycle and pregnancy test, which is ~15 days after conception, the neural tube is preparing for closure. Food fortification with folic acid is implemented in the United States, but has not yet been introduced in European countries [16-18].

CONCLUSION

Anencephaly is incompatible with life. The most important aspect is the prevention of its occurrence. The simplest way to reduce the incidence of anencephaly and other neural tube defects is to advise women of reproductive age to take folic acid supplements. It is important to avoid valproic acid in women with epilepsy. Fetal ultrasonography is the gold standard for detecting neural tube defects. Anencephaly should be detected as early as possible, in order to perform a timely termination of pregnancy.

REFERENCES

1. Santana MVMC, Canêdo FMC, Vecchi AP. Anencephaly: knowledge and opinion of gynecologists, obstetricians and pediatricians in Goiânia. Rev Bioét, 2016, 24(2):374–385. https://doi.org/10.1590/1983-80422016242138
2. Padmanabhan R. Etiology, pathogenesis and prevention of neural tube defects. Congenit Anom (Kyoto). 2006 Jun;46(2):55-67.
3. Mai CT, Isenburg JL, Canfield MA, et al. National Birth-DefectsPrevention Network, National population-based estimates for major birth defects, 2010-2014, BirthDefectsRes. 2019; 111: 1420-1435.
4. Sadler TW. Langman's Medical Embryology. 12th ed Philadelphia, USA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012. c2012 p.
5. Copp AJ, Adzick NS, Chitty LS, Fletcher JM, Holmbeck GN, Shaw GM. Spina bifida. Nat Rev Dis Primers, 2015, 1:15007. 10.1038/nrdp.2015.7
6. Mohd-Zin SW, Marwan AI, Abou Chaar MK, Ahmad-Annuar A, Abdul-Aziz NM. Spina bifida: pathogenesis, mechanisms, and genes in mice and humans. Scientifica (Cairo), 2017, 2017:29. 10.1155/2017/5364827
7. Karsonovich T, Brea CM, Munakomi S. Spina Bifida. [Updated 2025 May 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559265/
8. Centers for Disease Control and Prevention. Spina bifida: Facts. Retrieved July 24, 2025, from http://www.cdc.gov/ncbddd/spinabifida/facts.html
9. US Department of Health and Human Services National Institutes of Health . What causes neural tube defects (NTDs)? Retrieved July 24, 2025, from https://www.nichd.nih.gov/health/topics/ntds/conditioninfo/causes
10. Moretti, M. E., Bar-Oz, B., Fried, S., & Koren, G. Maternal hyperthermia and the risk for neural tube defects in offspring: Systematic review and meta-analysis. Epidemiology, 2005, 16(2), 216–219. Retrieved July 24, 2025, from https://journals.lww.com/epidem/fulltext/2005/03000/Maternal_Hyperthermia_and_the_Risk_for_Neural_Tube.10.aspx
11. Munteanu O, Cirstoiu MM, Filipoiu FM et al. Rom J Morphol Embryol 2020, 61(2):335–343, doi: 10.47162/RJME.61.2.03
12. Edwards L, Hui L. First and second trimester screening for fetal structural anomalies. Semin Fetal Neonatal Med. 2018 Apr;23(2):102-111
13. Medical Task Force on Anencephaly. The infant with anencephaly. N Engl J Med. 1990 Mar 08;322(10):669-74
14. Moussaoui KE, Bakkali SE, Ghrab I, Baidada A, Kharbach A. Anencephaly: Case report and literature review. J Gynecol Res Obstet 7(1): 005-007. DOI: https://dx.doi.org/10.17352/jgro.000096
15. Guideline: Daily iron and folic acid supplementation in pregnant women (2012) World Health Organization. Retrieved July 24, 2025, from https://www.who.int/publications/i/item/9789241501996
16. Obeid R, Holzgreve W, Pietrzik K. Is 5-methyltetrahydrofolate an alternative to folic acid for the prevention of neural tube defects? J Perinat Med, 2013, 41: 469-483
17. Czeizel AE, Dudás I, Paput L, Bánhidy F. Prevention of Neural Tube Defects with Periconceptional Folic Acid, Methylfolate, or Multivitamins? Ann Nutr Metab, 2011, 58: 263-271.
18. Greenberg JA, Bell SJ, Guan Y, Yu YH. Folic Acid Supplementation and Pregnancy: More Than Just Neural Tube Defect Prevention. Rev Obstet Gynecol, 2011, 4: 52-59