A case report of recurrent anencephaly and literature review

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Summary

Anencephaly is a rare congenital anomaly in which the forebrain, meninges, vault of the skull, and scalp all fail to form. We report a case of a 32-year-old gravida 2 woman with an anencephalic fetus detected at the 21st gestational week. She had a history of an intrauterine fetal death of an anencephalic fetus at the 20th gestational week two years before. We present the case and briefly review the literature.

Key words: Anencephaly; Neural tube defects; Spina bifida; Recurrence anencephaly; Prenatal diagnosis.

Introduction

Anencephaly is one of the common neural tube defects (NTDs) with an incidence, varying among registries, between 1/10,000 and 1/1,000 [1, 2]. The incidence is geographically and population dependent. From October 1995 to December 1996, anencephaly occurred in 11.6 of every 100,000 births in the United States [2]. Anencephaly is a disorder of embryogenesis caused by failure of the cephalic neural tube to close, resulting in a partial or complete absence of the brain. This neural tube defect is often associated with an absence of the skull above the eye level. Anencephaly with contiguous spina bifida is called craniorachiscisis. Synonyms are holoanencephaly and meroanencephaly [2]. Anencephaly like most of NTDs shows a multifactorial inheritance pattern. We present a case of recurrence anencephaly and we briefly review the literature on the main NTDs, anencephaly and spina bifida.

Case Report

A 32-year-old Caucasian woman (gravida 2, para 0) presented at the Department of Obstetrics & Gynecology, University Hospital of Crete, at the 21st week of gestation, with a history of intrauterine death of an anencephalic fetus at the 20th week of gestation two years before. The karyotype of this fetus had not been checked. The patient did not follow genetic counselling probably due to a low social-economic level, and she had not taken folic acid either periconceptionally or during the first trimester of this pregnancy. She had not received any medications for other medical conditions. The sonogram performed in our Maternal Fetal Medicine Unit was the first of the current pregnancy. This detailed sonographic scanning showed an anencephalic fetus with increased amniotic fluid and a small bladder. No other obvious structural defects were seen. Amniocentesis was performed and the fetal karyotype was normal. Both parents' karyotypes were examined and showed to be normal. After counselling, the parents decided to terminate the pregnancy. Intravaginal misoprostol was used for the pregnancy termination. Pathological examination revealed an anencephalic male fetus weighing 390 g (Figure 1, 2). Small cystic adenomatoid malformations of the lungs, dysplastic small kidneys, and a hypoplastic bladder were also seen.

Discussion

Neural tube defects are considered as relative common and severe malformations of the central nervous system. The most prevalent types in humans are anencephaly and myelomeningocele (spina bifida aperta) [3]. Anencephaly is a designation for congenital absence of the cranial vault with cerebral hemispheres completely missing or decreased to small masses attached to the base of the skull and is uniformly incompatible with survival [4].

Epidemiology

Affected infants are born throughout the world, and the birth prevalence is variable among countries [1, 2]. From October 1995 to December 1996, anencephaly occurred in 11.6 of every 100,000 births in the United States [2]. In parts of the British Isles the incidence may be as high as 1 in 100 births [1]. Rates of anencephaly at birth are highly influenced by the availability of prenatal diagnosis and elective pregnancy termination. There appears to be a female predominance among infants with anencephaly, and the prevalence of the defects is lowest in black infants. Anencephaly occurs more often in twin gestations than in singleton pregnancies (2% vs 1.4%) [5], especially in monozygotic twin pregnancies.

Etiology

From an embryological point of view, the brain and spinal cord are derivates of the neural tube, which is formed by fusion of the neural folds [6]. The process of neurulation is complex and involves proliferation of neuroblasts or matrix cells, differential development of the neuroepithelium and surface ectoderm, formation of the neural plate median hinge point, apical constriction of neuroepithelial cells, and expansion of the mesoderm and extracellular matrices. Possibly NTDs in humans result from the combined effects of genetic and environmental

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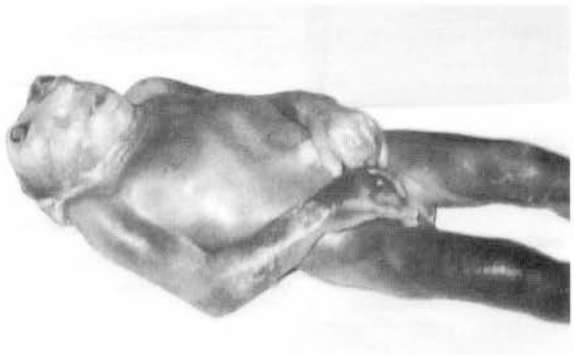
Fig. 1



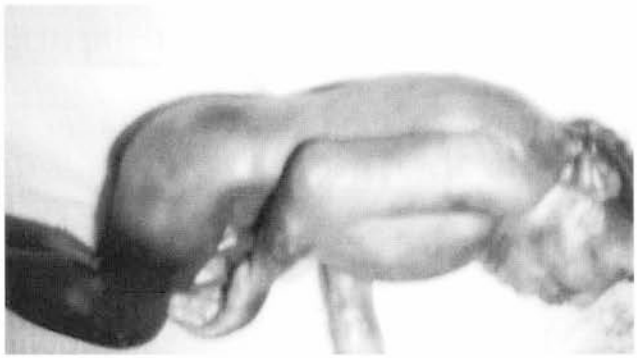


Fig. 2

Figures 1 & 2. — An anencephalic male fetus weighing 390 g, immediately after the pregnancy termination.

influences, and as such are a classic example of a multifactorial disorder. Identifying the genetic factors is critical for characterizing the interactions between genes and the environment, and understanding these interactions will provide the basis for designing novel preventive strategies and for offering accurate reproductive risks to couples. The genetic factors will likely involve aberrant variations in genes, key for the normal closure of the neural tube [7]. Thus, the etiology of anencephaly is believed to be multifactorial, involving both genetic and environmental factors. Possible environmental associations include maternal hyperthermia, radiation, maternal diabetes, the use of anti-epileptics during pregnancy, and low socioeconomic class. This complex group of multifactorial events may result in disregulation of the primary developmental field, causing problems in axiation development and thus in the midline field [8]. This is also evidence of the importance of genetic factors. Geographic and temporal variation in the prevalence of anencephaly is well documented [9]. The geographic variation seen for NTDs also argues in favor of a strong genetic contribution. The northwest of the British Isles has the highest recorded prevalence rate in the world, with approximately 1% of births affected by anencephaly or spina bifida, while this figure is about five times lower in most regions on which reliable data have been published [10]. The most significant environmental risk factor identified to date is folic acid. The evidence documenting the preventative effect of folic acid on the incidence of anencephaly is extensive, offering an opportunity for prevention. Originally it was thought that the folate deficiency would be a surrogate to lower socioeconomic status, based on the findings in Britain [11, 12]. However, South America as an example has low prevalence rates for anencephaly and spina bifida in spite of being an underdeveloped region, where even lower incomes and poorer diets than those of the British low social classes are to be expected [13]. This evidence supports the potential importance of the genes involved in folate metabolism.

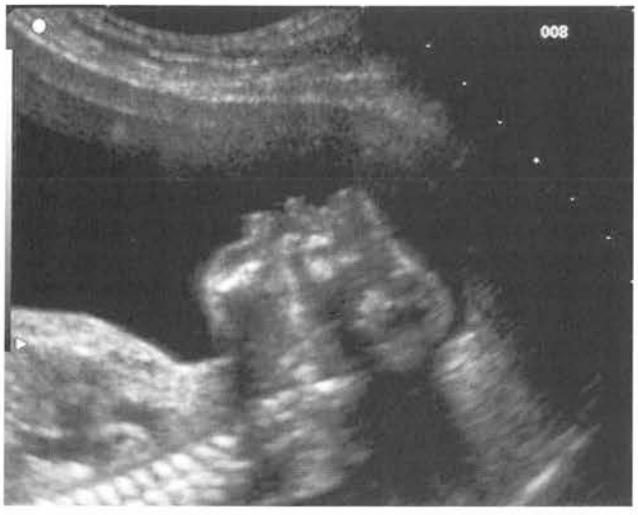
More than 80 mutations in a variety of genes have been identified and linked to a variety of rodent NTDs, implicating more than 100 genes directly or indirectly in neural tube formation. Unlike the majority of human cases, many of these mutants show autosomal recessive inheritance and, in addition to NTDs, these mice present other associated anomalies. Moreover, the penetrance and expression of many of these mutations are affected by the genetic background, which can increase the susceptibility to teratogen-causing NTDs, consistent with multifactorial inheritance [7]. Methylenetetrahydrofolate reductase (MTHFR) is the most studied gene, but the evidence suggests that additional genes other than MTHFR may be responsible for an increased risk of NTDs [14]. Other folate metabolism genes that have been studied include glutamate carboxypeptidase II (GCPII), reduced folate carrier 1 (RFC1), folate receptor-alpha (FR-a) and beta (FR-h), methionine synthase (MS), methionine synthase reductase (MTRR), and methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) [15-20]. Differences in the molecular mechanisms of the folate metabolism genes between spina bifida and anencephaly are yet to be approached.

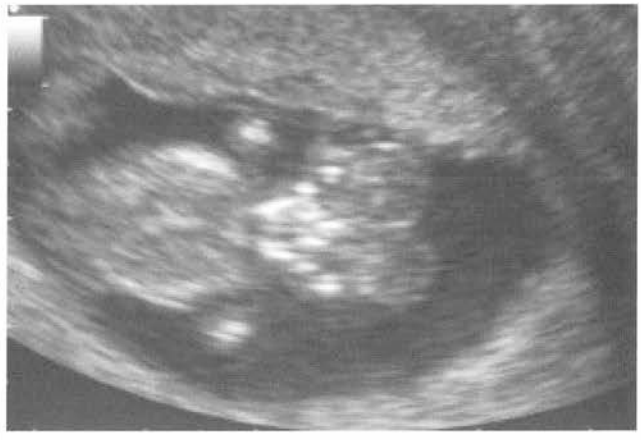
Risk factors

Family history of NTDs is the most important risk factor. NTDs and anencephaly are multifactorial in inheritance, and thus the risk to a first-degree relative is approximately 2-3%, which is 20 to 30 times higher than the risk of NTDs in the general population. The level of risk is directly related to the number of affected relatives and their degree of relatedness to the fetus, and should be estimated individually for each family [21].

Recurrence risk

Distinction should be made between isolated NTDs and those that are part of a syndrome. Because the etiology is heterogeneous, the recurrence risks depend on the underlying cause. Common specific disorders associated with NTDs, and less commonly with anencephaly, are single-gene defects such as Meckel's syndrome, an autosomal recessive condition with a recurrence risk of 25%. Trisomies, triploidies, unbalanced and balanced rearrangements can also be associated with NTDs, and have different recurrence risks. Therefore, it is crucial to determine the etiology of NTDs in order to provide accurate counselling.





Figures 3 & 4. — Saggital and coronal view of a fetus with exencephaly at 12 weeks' gestation. Although the brain is present, the skull is absent.

In NTDs occurring without other syndromes, the recurrence risk for siblings is approximately 2-5% (giving an approximate value between 20 and 50) [22], which represents up to a 50-fold increase over that, observed in the general population. Khoury *et al.* have shown that for a recurrence risk to be this high, an environmental teratogen would have to increase the risk at least 100-fold to exhibit the same degree of familial aggregation, making a genetic component essential. Such potent teratogens are extraordinarily rare [23].

The first publication concerning the recurrence rate of anencephaly was made during 1950 by Record and McKeown [24]. They estimated that the empiric risk of recurrence is about 2%. In 1968 Yen and MacMahon studied the recurrence of anencephaly in families, and concluded that the findings were explained by a persistent environmental factor as adequately as by genetic factors [25]. In 1995 Zlotogora stated that among families from Iran or Iraq, anencephaly is the most prevalent NTD [26]. He suggested the existence of a major autosomal recessive gene responsible for anencephaly in this community. In 1988 Hal *et al.* estimated that the recurrent risk of NTDs were seen in 2.2% of the siblings of anencephalic probands, in 7.8% of the siblings of probands with high spina bifida but in only 0.7% of the siblings of probands with low spina bifida, and in none of the siblings of probands with craniorachischisis, encephalocele, or multiple NTDs ($p < 0.001$) [27].

Diagnosis

Anencephaly is diagnosed after viewing the structural defect either during prenatal ultrasonography or at birth. Accompanying malformations can be craniofacial, gastrointestinal, renal, and cardiac, and can include associated single-gene or chromosomal syndromes. The differential diagnosis should be made from an amniotic band disruption sequence, from acrania and from acalvaria [2]. Anencephaly can be diagnosed in the first trimester, when the skull cannot be seen due to the absence of the cranial vault, whereas the face itself, including the orbits, can be imaged. When brain remnants appear flat, the term anencephaly is used. When brain remnants appear as an irregular bulging structure, the term exencephaly is usually preferred (Figures 3 & 4). Prenatal diagnosis is obvious in the second trimester (Figure 5). In the first trimester, a round shaped structure corresponding to the exposed brain can be misleading if ultrasound is performed too early, at eight to ten weeks. This underscores the need to perform first trimester ultrasound at 12-13 weeks, when it becomes possible to analyze anatomical structures of interest. In recent years, NTDs, and particularly anencephaly have been detected prenatally; maternal serum screening has become the standard of care in many centers, and ultrasound resolution and skill are optimized.

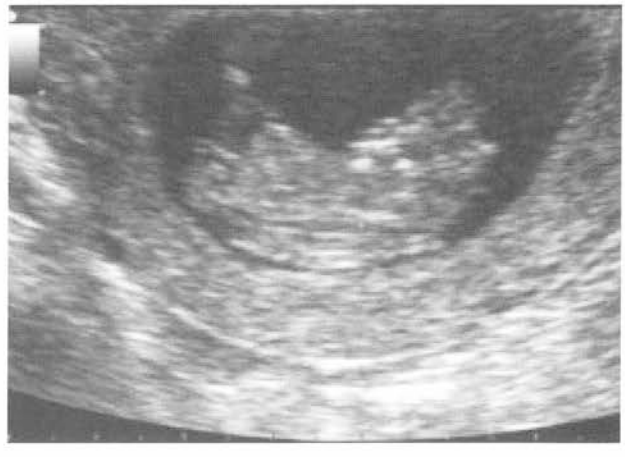


Figure 5. — Anencephaly at 22 weeks' gestation. No visible brain and skull is present superiorly to the level of the orbits.

Isolated defect or accompanied anomaly of malformation syndromes?

Anencephaly occurs more frequently as an isolated defect. When associated with other unrelated anomalies, the most frequent defects are omphalocele, diaphragmatic hernia, and kidney anomalies, facial anomalies, spina bifida, hypoplasia of male external genitalia, hypoplastic adrenal glands, intrauterine growth retardation, thymus enlargement, and amniotic bands [28-32].

Anencephaly as well as other NTDs can occur as part of malformation syndromes resulting from known chromosomal abnormalities (e.g., trisomy 13,18 and 21) and single-gene disorders (e.g., Meckel-Gruber and Waadenburg syndromes) [33]. The incidence of chromosome abnormalities among fetuses with NTDs has not been well delineated and fetal chromosome analysis and autopsy are not routinely performed when NTD is detected prenatally. Isolated NTDs were often excluded or under-represented because they were not thought to be associated with chromosomal abnormalities, and therefore not an indication for karyotyping. In a study by Hume *et al.*, 106 NTDs were studied, 44 with anencephaly and 62 with open spina bifida [34]. Six of 106 (5.7%) had chromosome abnormalities including five trisomy 18 and one inherited marker chromosome. They found an overall aneuploidy rate of 5-6% in NTDs prenatally diagnosed by ultrasound. In their study, there was a marked difference in the aneuploidy rate between fetuses with isolated NTD (2%) and those with multiple congenital anomalies (24%). The most common chromosome abnormalities reported to be associated with neural tube defects include ring 13, trisomy 18, trisomy 21 triploidy, tetraploidy, dup(2)(pter→p13), dup(3)(q23→qter), dup(11) (q23→qter), dup(22)(pter→q11), del(13)(q14→qter), ring 20, and mosaic trisomies 8, 9, and 14 [35]. Nickel and Magenis reported deletion of 22q in three of 295 patients with NTDs [36]. However, the incidence of 22q deletion may be higher than reported since only 16 children, all with additional clinical traits and/or positive family history, actually had molecular cytogenetic testing. Harmon *et al.* have suggested that a significant proportion of NTDs (12-20%) are not simply multifactorial in origin and therefore karyotype analysis is warranted [37]. They reviewed 55,260 obstetrical ultrasounds performed at the university prenatal diagnostic center. They found that 16.3% of the fetuses with isolated NTDs had abnormal karyotypes. They compared this to the theoretical risk of chromosomal anomalies in the same population based solely on maternal age (0.3%) and found statistical significance. Babcoock *et al.* noted that in NTDs prenatally detected by ultrasound the 'isolated' type is overestimated as some associated abnormalities, such as IUGR, are difficult to diagnose at 16-18 weeks when an anatomic scan is usually performed [38]. Hume *et al.* stressed the need for a thorough ultrasound examination to search for anomalies associated with the NTD [34]. They also recommended fetal karyotyping for prognosis and management of the abnormal and future pregnancy, pointing out that if chromosomal causes are excluded, preconception folic acid may be more likely to have an impact on recurrence risk. The diagnosis of a chromosome abnormality associated with NTD has important implications for recurrence risk and prenatal diagnosis, not only for the parents but also potentially for other relatives. Three quarters of mothers of affected fetuses have polyhydramnios [2]. Elevated maternal serum or amniotic fluid α-fetoprotein may be associated with anencephaly or other neural tube defects and warrants ultrasonographic examination of the fetus.

Our case recalls the need for complete anatomic and cytogenetic studies when an NTD is discovered. The obstetrical, perinatal, and genetic management of the current and of future pregnancies depend on these investigations. NTDs, even isolated, could be associated with aneuploidy and occasionally unbalanced structural chromosomal rearrangements. We therefore conclude that all NTDs should be karyotyped because of implications for pregnancy management, as well as the need of appropriate recurrence risk counselling.

Treatment

As anencephaly is uniformly lethal, no treatment exists. It is estimated that half of affected infants are stillborn. Moreover, liveborn infants usually die within 48 hours of delivery, unless medical support is initiated [2]. The American Academy of Pediatrics and the American Heart Association have indicated that withholding resuscitation in the delivery room is an ethical option [39]. Thus, primary prevention of anencephaly is the most promising medical intervention available. Increasing daily folic acid intake by women before and during the first trimester of pregnancy can decrease the risk of neural tube defects, including anencephaly, by 50% [40, 41]. The United States Public Health Service recommends that all women capable of becoming pregnant take 0.4 mg of folic acid daily [41]. Women who have had a child with a neural tube defect should take a higher daily dose (4 mg) of folic acid periconceptionally to decrease the risk in subsequent pregnancies.

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