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Anencephaly: A Neural Tube Defect – A Review

Priya Gupta[1*], Parminder Nain[1], Jagjit Singh[2]

1. M.M College of Pharmacy, Maharishi Markandeshwar University, mullana, Ambala (Haryana).

2. Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh..

ABSTRACT

Neural tube defects (NTDs) are one of the commonest birth defects. They form a spectrum of disease ranging from anencephaly to spina bifida occulta. Anencephaly is a cephalic disorder that occurs when the cephalic (head) end of the neural tube fails to close, resulting in the absence of a major portion of the brain, skull, and scalp. However few studies have systematically looked into the etiopathogenesis of anencephaly which mainly includes nutritional deficiencies and genetic predisposition. Efforts are a foot for universal food fortification with folic acid in the hope of preventing NTDs. So we hereby conclude that caution should be exercised before widespread of anencephaly or the NTDs.

Keywords: Neural tube defect, Anencephaly

*Corresponding Author Email: priya_gupta1919@yahoo.com

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INTRODUCTION:

Neural tube defects (NTDs) top the list of birth defects in India contributing to both morbidity and mortality. The National Institute of Neurological Disorders and Stroke conducts and supports a wide range of studies that explore the complex mechanisms of normal brain development[1]**.** Neural tube defects (NTDs) are one of the commonest malformations seen forming a spectrum of disease ranging from anencephaly to spina bifida occulta[2]. These are devastating conditions as most of the lesions (myelomeningoceles, myelocele etc.) are always associated with neurological deficits producing varying degree of limb paresis/paralysis, bladder and anorectal incontinence. The number of NTDs diagnosed is progressively increasing with the advent of prenatal screening with ultrasound and maternal serum alphafetoprotein [3]. The knowledge gained from these fundamental studies provides the foundation for understanding how this process can go awry and, thus, offers hope for new means to treat and prevent congenital brain disorders including neural tube defects such as anencephaly[4.]

ANENCEPHALY:

Anencephaly is a serious birth defect in which a baby is born without parts of the brain and skull. It is a type of neural tube defect (NTD). These are birth defects that happen during the first month of pregnancy, usually before a woman knows she is pregnant. As the neural tube forms and closes, it helps form the baby's brain and skull (upper part of the neural tube), spinal cord, and back bones (lower part of the neural tube). Anencephaly happens if the upper part of the neural tube does not close all the way. This often results in a baby being born without the front part of the brain (forebrain) and the thinking and coordinating part of the brain (cerebrum). The remaining parts of the brain are often not covered by bone or skin[5] . An anencephalic new born can be seen in figure 1.

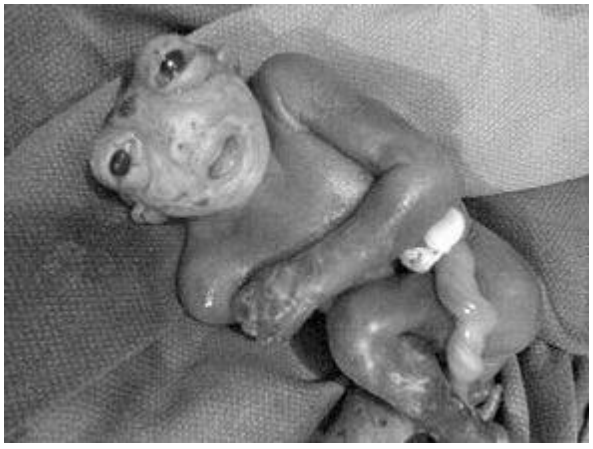

Figure 1: An Anencephalic New Born

Occurrence

Unfortunately, almost all babies born with anencephaly die shortly after birth. The reported NTD incidence in India varies from 0.5 to 11/1000 births while the incidence in the USA and Europe is reportedly below 1/1000, with progressive decline with periconceptional folate fortification[6]. Centres for disease control and prevention (CDC) estimates that each year, about 1 in every 4,859 babies in the United States will be born with anencephaly[7].

Prognosis of Child with Anencephaly

The infant is usually blind, deaf, unconscious, and unable to feel pain. The eyeballs can protrude because of a malformation of the eye-sockets. Although some individuals with anencephaly may be born with a rudimentary brain stem, the lack of a functioning cerebrum permanently rules out the possibility of ever gaining consciousness. Reflex actions such as respiration (breathing) and responses to sound or touch may occur. Children born with anencephaly are only expected to live a few hours, days, or weeks. Seventy-five percent of anencephalic births are still births, while the remaining 25 percent of infants die shortly thereafter. Anencephaly affects girls more than boys[5].

Etiology

The cause of anencephaly is not known, though it is believed to be a mixture of environmental and genetic factors. Although it is believed that the mother's diet and vitamin intake may play a role, scientists believe that many other factors are also involved[8]**.** The nervous system becomes evident on post-ovulation day 18, and neural tube closure occurs during days 22-28. Thus, NTDs occur so early that most women are unaware of their pregnancy. Therefore, any advice regarding dietary modification, supplementation, and food fortification should be in the periconceptional period i.e. beginning at least 1 month before conception and continuing through the first trimester [9-13].

Centers for disease control and prevention (CDC) works with many other researchers to study risk factors that can increase the chance of having a baby affected by anencephaly. Scientists believe that many factors such as genes, behaviors, and things in the environment are involved[14]. CDC researchers have reported important findings about some factors that affect the risk for anencephaly:

- Low intake of folic acid before getting pregnant and in early pregnancy increases the risk of having a pregnancy affected by neural tube defects, including anencephaly. There has been a 27% decline in pregnancies affected by neural tube defects since the U.S began fortifying enriched grains with folic acid[15].

- Some medicines (valproic acid, antimetabolic drugs and others) lower Folic Acid levels, hence taking those increases the risk of giving birth to a child with anencephaly[16].
- Chromosomal abnormalities, single-gene mutations, and teratogenic causes are indentified in fewer than 10 percent of affected infants[17].
- Paternal Occupation and Anencephaly: It has been suggested that paternal occupational exposures to pesticides and solvents increase the risk of neural tube defects in offspring. With the use of Texas live birth, fetal death, and linked live birth-death records, the authors conducted a population-based case-control study among 1981–1986 Texas births to examine the association between paternal occupation and anencephalic births. Fathers employed in occupations associated with solvent exposure were more likely to have offspring with anencephaly[18]. Here are the possible factors enumerated in Table 1.

Diagnosis*:*

Diagnostic tests performed during pregnancy to evaluate the baby for anencephaly include the following:

- **Amniocentesis**- a test performed to determine chromosomal and genetic disorders and certain birth defects. The test involves inserting a needle through the abdominal and uterine wall into the amniotic sac to retrieve a sample of amniotic fluid[19].
- **Alpha-Fetoprotein (AFP)** - a protein produced by the fetus that is excreted into the amniotic fluid. Abnormal levels of alpha-fetoprotein may indicate brain or spinal cord defects, multiple fetuses, a miscalculated due date, or chromosomal disorders. AFP levels can be measured via a maternal serum screening test (blood test). If levels are high, there is a risk that the child may be suffering from anNTD[20].

- **Ultrasound**

  (Also called sonography)- a diagnostic imaging technique that uses high-frequency sound waves and a computer to create images of blood vessels, tissues, and organs. Ultrasounds are used to view internal organs as they function, and to assess blood flow through various vessels. Anencephaly can be reliably diagnosed at 11-14 weeks of gestation by ultrasound scan[20].

BLOODTESTS

Prevention*:*

Hyperhomocysteinemia:

Plasma homocysteine (hcy) is considered to be a good integrated marker of folate and vitamin b_{12}during pregnancy attributed to increased glomerular filteration rate (gfr) during pregnancy, lower plasma albumin that binds to hcy and increased cortisol level during pregnancy. Inherited defects in enzymes of 1-carbon metabolism (*e.g.* methionine synthase) or cofactors such as folates and/or vitamin b_{12} cause abnormal hcy metabolism resulting in hyperhomocysteinemia[21]. This necessitates use of different cut-off points for hyperhomocysteinemia during pregnancy and 10 mmol/l has been used as the cut-off[22].

- The dosage of folic acid recommended are: to avoid occurrence of ntds- 0.4 mg/day and to avoid recurrence of ntds- 4 mg/ day. It has been observed that by this folate supplementation dosage, the ntds occurrence rate has decreased by 58% and the recurrence rate by 95% [23].
- The principal dietary sources of folate are leafy green vegetables, legumes (beans, peas), citrus fruits (juices), liver and whole bread .the folate content of these natural sources is variable with less bioavailability as folate in these is present as polyglutamates and it needs to be converted to monoglutamates for its utilization. all synthetic forms of folic acid contain only monoglutamates[24].

Role of Folic Acid in Ntd Prevention:

Folic Acid is a coenzyme. It plays an important role in many metabolisms. The developing unborn child needs it to grow cells, tissue and organs. During that phase, the folic acid requirements are higher than usual.

- Recent research on NTD pathogenesis suggests that disorders linked to methioninesynthase activity could be one of the factors involved. This enzyme transforms homocysteine into methionine. To do so, it needs a methyl group which is provided by Folic Acid intake. If this transformation fails to take place, be it because of an enzyme anomaly or lack of Folic Acid, homocysteine levels increase. This would appear to prevent the closure of the Neural Tube. An additional intake of Folic Acid, coupled with an intake of vitamin B_{12} can rectify this anomaly which is in part connected with enzymes. Other studies have also shown that further anomalies such as heart malformations, lift and palate clefts and urethra malformations can be prevented by an additional intake of Folic Acid [25].

RECENT STUDIES REVEALING ABOUT ANENCEPHALY:

- The incidence rates of anterior neural tube defects, anencephaly appears increased among twins compared with singletons. Studies suggest that twin pregnancies conceived by assisted reproductive technology (ART) constitute a high-risk group for anencephaly, due to a possible synergistic effect of twinning and ART[26].
- FOXN1 is a member of the class of proteins involved in the development and differentiation of the central nervous system. We identified a human fetus homozygous for a mutation in FOXN1 gene who lacked the thymus and also had abnormal skin, anencephaly and spina bifida. Moreover, we found that FOXN1 gene is expressed in mouse developing choroid plexus. These observations suggest that FOXN1 may be involved in neurulation in humans[27-30].
- Women who have had histories of reproductive losses, especially miscarriages, should be a priority group for the primary and secondary prevention of neural tube defects[31, 32].
- Polyhydramnios appeared in 38 per cent of the anencephalic pregnancies of recent studies, while 15 per cent of the deliveries were complicated by placenta praevia[33, 34].
- Edwards, in an extensive study of congenital malformations of the central nervous system in Scotland, noted that "improved social conditions which have led to a great reduction in most other causes of stillbirths have not influenced the year to year rate of anencephalic births [35].
- The abortion rate in mothers who bore an anencephalic child was 37 per cent in the present study. Hertig in 1954 reported that the abortion rate of anomalous fetuses is about four times the incidence of anomalous children born either alive or dead [36].
- In a study of 181,548 stillbirths, Ciocco4 found the total male stillbirths to be 103,642, and the total female stillbirths, 77,906. When Ciocco divided the total stillbirths into subgroups according to the cause of death, in only one category, malformations, were there more female stillbirths than male. Of 10,301 stillbirths due to malformations, the ratio was 748.9 males to 1,000 females. It is of interest that in the other categories for causes of stillbirths, such as maternal disease, fetal injury and anomalies of the placenta and cord, in which environmental factor rather than genetic disease would be the primary consideration, the stillbirth sex ratio showed a predominance of males[37].

Anencephalic Newborns: A Source of Transplantable Organs

A severe shortage of transplantable organs exists for infants and children with life-threatening cardiac, renal, and hepatic disease. Newborns with anencephaly, a uniformly fatal neurological lesion, have been successfully used as sources of hearts and kidneys for transplantation. Both the

number of anencephalic births each year as well as evidence that most of the organs from anence phalics are morphologically and functionally normal suggest that anencephalics could significantly contribute to the number of available infant organs[38].

Table 1: Etiology of Neural Tube Defects[39]

Etiology	Examples
Nutritional	Folate , B_6 and B_{12} deficiency, Zn deficit
Maternal illness	Diabetes
Teratogenic	Anti-epileptic drugs: phenytoin and valproate, Warfarin, hypervitaminosis A & D, addictions like coccaine & alcohol
Chromosomal	Trisomy 13 and Trisomy 18
Single gene effects	meckel- gruber syndrome
Complex eco-genetic	predisposing polymorphisms in genes eg: MTFR C677T polymorphism

CONCLUSION:

In the above article the major thrust of primary prevention of anencephaly has been on nutritional supplementation with folate. But the discovery of numerous genetic models of NTDs, and a much clearer understanding of the complexities of folate and its biochemical pathways, the exact mechanism by which each of these factors interacts in complex ways to produce a human myelomeningocele remains a mystery.

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