Neural tube defects are rare in industrialized countries

In the United States, the incidence of combined causes of neural tube defects is 1.5/1000 live births (5). These causes include various environmental chemical teratogens, improper nutritional diets, and inherited genetic predisposition. The parents of an affected infant, identified as carrying a relatively large number of high-liability genes, have about a 1/30 chance of producing a 2nd affected offspring. Similarly, an affected parent with a neural tube defect has a increased 3 to 4% chance of having an affected child (6). In the relatively rare instance where a couple has had 2 affected children, the risk for a 3rd rises further (7 to 8%).

Vitamin A is important in many biological systems

Vitamin A consumption is important for vision, reproduction, cell membrane integrity, and cell growth and differentiation (24). Although Vitamin A deficiency is uncommon in industrialized nations, many other causes can also produce similar effects. Topical use of many synthetic creams containing Vitamin A produce such effects, especially during the first trimester of pregnancy (2). Some of the complications that have occurred extend from multiple congenital malformations to spontaneous abortions.

Vitamin A (retinol) is fat soluble and is found mainly in fish liver oils, liver, egg yolk, butter, and cream. Green leafy and yellow vegetables contain beta-carotene and other pro-vitamin carotenoids. Upon entering the small intestine they undergo central fission of the molecule in the mucosal cells to form retinol.

Vitamin A is the term used to describe the fat soluble vitamin, all trans retinol. Several synthetic forms such as 13-*cis* Retinoic Acid (isotretinoin), etretinate (an ethyl ester) and etretin (a carboxylic acid) have been developed to treat various dermatological disorders.

Most of the body's vitamin A is stored in the liver as retinyl palmitate. It is released into the circulation as retinol bound to a specific protein, retinol-binding protein (RBP), and is also attached to prealbumin (transthyretin). The 11-cis isomer of retinal (vitamin A1 aldehyde), combined with a protein moiety, forms the prosthetic group of photoreceptor pigments in the retina that are involved in night, day, and color vision.

Too much of a good thing can cause deleterious effects

First licensed in the United States in September, 1982 to treat cystic acne, Isotretinoin, (13-cis Retinoic Acid) a congener of Vitamin A (17), was taken off the market. Within its first year as a commercial treatment of cystic acne, it was demonstrated to cause serious teratogenic effects in the developing fetus (12). Exposure to Isotretinoin in the second to fifth week of pregnancy causes an increase in spontaneous abortions, and at least one major malformation in about 25% of their offspring (6). Over 70% of infants exposed prenatally with RA, through maternal treatment of acne, have been identified with a severe characteristic pattern of craniofacial, central nervous system and cardiovascular abnormalities (9, 20).

Contrary to what many researchers had feared, doses of vitamin A commonly taken during pregnancy do not increase the chances that a woman will have a child with a birth defect, according to a study conducted by the National Institute of Child Health and Human Development (16). Taking daily doses of between 8,000 and 10,000 International Units (I.U.) of

vitamin A during pregnancy does not appear to cause birth defects. The Recommended Daily Allowance (RDA) for vitamin A is 2,670 International Units.

Birth defects in humans have been reported by the ingestion of as much as of 25,000-500,000 IU from a single accidental dose in the second month of pregnancy. These defects reinforce the ill effects of isotretinoin, etretinate, or doses of Vitamin A greater than 15,000IU/day during pregnancy (10).

The degree of teratogenesis is time-dependant

Teratogens may act by a relatively limited number of pathogenetic processes. They may produce cellular death (apoptosis), alter tissue growth (hyperplasia, hypoplasia, or asynchronous growth), or they may interfere with cellular differentiation or other basic morphogenetic processes (dysplasia).

The teratogenic potential of an agent varies over a wide spectrum. Table 1 is presented to indicate the various stages of embryogenesis. It explains why neural tube defects are so prevalent within the first two to three weeks of development, when the mother is exposed to high concentrations of Vitamin A. This variability in expression could be the result in differences in the dose of the agent, timing of exposure, or host susceptibility, or could be due to interactions with other environmental factors (14).

The teratogenic potential of Vitamin A (retinol) is well established in numerous reports and in experimental animals (18). Treatment of pregnant rodents with excessive doses of Vitamin A results in greatly increased rates of fetal reabsorption and still births (4). The large doses of Vitamin A given during the critical period of organogenesis results in abnormalities including absence of the brain, ocular abnormalities, cleft palate, extremity malformations, and labial fissures. Current Recommendations for Vitamin A intake during pregnancy include a recommended daily allowance of 800 retinol equivalents per day (2700 IU, or 4,800 m g beta carotene) (7).

Major Events During Human Embryonic Development

Day 7 Implantation

Day 16 Three germ layers become distinct

Day 19 Neural Plate formed

Day 27 Neural Tube closes

Day 30 Limb buds appear

Weeks 4-5 Branchial arches, clefts, pouches, and optic vesicle formed

Weeks 5-7 "Mature heart and kidneys formed

Week 7 Hard palate fused, upper lib formed, physiological herniation of intestines

Week 8 Mature limb architecture formed

Weeks 7-10 Return and rotation of intestines into abdominal cavity

Weeks 10-16 Hair patterning established

Weeks 10-13 Dermal ridges and creases formed

Source: Schardein, J. Chemically Induced Birth Defects: Principles of Teratogenesis Applicable to Drug and Chemical Exposure, 1997

Neural tube defects can be easily detected in pregnant women

Maternal Serum Alpha-Fetoprotein (Msafp) screening for neural tube defects (NTDs) and other fetal abnormalities should be offered to all eligible pregnant women (23). MSAFP programs were developed to determine those pregnant women with sufficient risk to justify amniocentesis (about 1 to 2% of those screened). However, MSAFP does not detect every fetus with NTD; about 80% with open spina bifida and 90% with anencephaly will be detected (21). Accurate gestational age assessment at the time the sample is obtained is essential. If ultrasound (US) assessment of gestational age is done prior to MSAFP sampling fewer false-positives will be identified.

With an elevated MSAFP, the pregnancy is at increased risk for NTD. Ultrasound (US) examination is the next step in evaluation. Other reasons for elevated MSAFP demonstrable by US include underestimation of gestational age (20 to 30%), multiple gestation (5 to 15%), threatened abortion (10%), fetal demise, and other rare congenital abnormalities.

In about 2% of the originally screened population, US cannot identify a cause for the elevated MSAFP. Unless the diagnosis by US is certain, amniotic fluid alpha-fetoprotein (AFAFP) remains the standard method for detection of NTDs. Virtually all cases of anencephaly and 90 to 95% of spina bifida will have elevated AFAFP.

Congenital abnormalities can be multifactorial

There are five major congenital categories to which syndromes can be grouped into: chromosomal, single gene mandelian), multifactorial (interaction of genetic and environmental), teratogenic (environmental insults), and uknowns. Only the first three can be categorized primarily as genetic. Many of the common isolated congenital anomalies (e.g., neural tube defects) are associated with multifactorial inheritance. However, this mode of inheritance is not the only responsible cause for multiple congenital anomalies and can be ruled out when more than one defect is present (11).

Determining that a group of multiple congenital anomalies has a genetic etiology depends on demonstrating an actual abnormality in genetic material, diagnosing a known genetic condition, or providing evidence of inheritablility.

The first step in mutagenesis frequently begins at the Retinoic Acid Receptor

In 1995, the gene responsible for many cases of neural tube defects was identified (19). This discovery supplies us with the genetic component that leads to NTDs. The aberrant gene

probably accounts for about 15 percent of NTDs. Since the metabolic cause of the abnormality has been describe much research attention is now being focused on how the function of growth factors contribute to the expression of Hox genes (1). While these genes are not responsible for all cases of mutagenesis, they do occur roughly three times more often in people with NTDs than people without NTDs (8).

Development of the embryo occurs according to the specific pattern and of gene expression. These expressions are affected deleteriously by Retinoic acid (RA) when it binds to nuclear retinoic acid receptors (RARs), activating them to induce or suppress transcription of the hox genes (8). Although RA has a physiological role, exposure to exogenous amounts can lead to inappropriate gene expression if it occurs during organogenesis. RA has been shown to alter the expression pattern of TGFa , TGFb -1 and TGFb -2 in embryonic palate (3). In addition, the mRAR-b -2 gene has been altered by RA to produce limb deformation (15), while the RAR-b -2 and Ghox-8 gene may induce programmed cell death (apoptosis), (8).

It now is apparent that the mere intake of excessive retinoic acid is no longer an elusive, uncharacterized pathological abnormality. While neural tube defects were once considered a enigmatic medical and public health problem, we now know the primary cause of NTDs. Through large epidemiological studies, we were able to implicate Vitamin A and its congeners.

Now we are in a new era, a time period where we can now further investigate the cellular, molecular and genetic factors causing NTDs. With these new tools at our disposal and with the international intellectual zeal scientist have in treating genetic defects we can only look forward to the possibility of eliminating neural tube defects completely, and perhaps, by screening and treating the fetus in utero.

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