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ISSN 2544-1361 (online); ISSN 2544-2406
doi: 10.15584/ejcem.2017.2.9

http://www.ejcem.ur.edu.pl/en/
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2017; 15 (2): 151–156

REVIEW PAPER

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Neural tube defects: risk factors and prevention

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ABSTRACT

Neural tube defects are abnormalities that can occur in the brain (anencephaly, encephalocele), spine (spina bifida, myelomeningocele, myelodysplasia), both brain and spine (craniorachischisis) or spinal column of a developing embryo that are present at birth. They arise when the neural tube, the embryonic precursor of the brain and spinal cord, fails to close during neurulation. Many cases of neural tube defects occur worldwide each year in more than 300,000 newborn babies and are a significant cause of infant death and lifelong disability. Most neural tube defects are preventable. The prevalence of these abnormalities has decreased in the past 20 to 30 years due to periconceptional folate supplementation, food fortification and decreased exposure to environmental factors. Women who are planning to conceive should be informed about the importance of folic acid in fetal development and encouraged to take 400 µg/day of folic acid supplements. Numerous research studies have shown that taking this dosage of folic acid before and during early pregnancy significantly reduces the risk of neural tube defects. For that reason it is important to increase the awareness of women in childbearing age about the necessity of primary prevention and folate intake which is a strong factor that has wide implications in public health in reducing the mortality and morbidity of offspring.

Key words. neural tube defects, NTD, anencephaly, spina bifida

Introduction

Neural Tube Defects (NTD) are one of the most common and most serious developmental disorders of the fetus and the newborn. The total prevalence of NTD in Europe is 9.1 (3.34 identified as anencephaly and 4.63 by spina bifida) per 10,000 births. In Poland, with data only from Wielkopolska, this condition affects 9.25 children per 10,000 births (1.61 anencephaly and 6.59 spina bifida).[1]

The neural tube is a transient structure formed during embryonic development of the central nervous system which consists of the brain and spinal cord. Neural tube closure (NTC) or neurulation is one of the most complex morphogenetic events that occurs during embryogene-

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

Received: 10.01.2017 | Accepted: 19.05.2017
Publication date: June 2017

Podgórski R, Stompor M, Kubrak T, Podgórska D. *Neural tube defects: risk factors and prevention*.Exp Med. 2017; 15(2):151–156. doi: 10.15584/ejcem.2017.2.9

sis. The process begins in humans at a very early stage of fetal development, approximately day 17 postfertilization. The entire neurulation process requires 10 days and occurs during weeks 3 and 4 postfertilization. During the neurulation process, the neural plate is folded, elevated, apposed, closed and fused at the dorsal midline, thereby separating non-neural ectodermal tissue from the neural tube.[2,3] Neural tube closure is initiated by signals from the primitive node (the organizer) and notochord that cause the overlying epiblast to become thickened forming the flat neural plate.[4] By day 19, the plate has lengthened and the edges in the cranial region begin to elevate on either side, forming the neural groove in the midline. Soon the edges of the folds begin to elevate further, rolling into a tube to meet each other and fuse. Fusion begin at the level of the fifth somite and proceeds in cranial and caudal directions. The cranial and caudal openings of the tube, created by the initiation of fusion, are known as neuropores. Closure of the cranial neuropore occurs on day 25, followed by closure of the caudal neuropore on approximately day 27.[3,5] Disruption of this dynamic and complex process can caused neural tube defects. The process of NTC is affected by various genetic and non-genetic factors. More than 200 genes are known to cause NTD in mice. These genes are involved in folic acid metabolism, glucose metabolism, retinoid metabolism, and apoptosis.[6]

Most nonsyndromic NTD is thought to be of multifactorial origin with influence of both genetic and environmental factors.

Risk factors

Nutritional

Folic acid (folate) is one of the water-soluble B vitamins that plays a significant role in the occurrence or recurrence of NTD. Folic acid is necessary for normal cell growth and replication, production and maintenance of new cells, DNA synthesis and RNA synthesis through methylation, and for preventing changes to DNA. Folate serves as a 1-carbon donor for the synthesis of purines and thymidine as well as in the remethylation cycle of homocysteine to methionine.[7,8] There are many studies that have confirmed the crucial role of folic acid supplementation during conception on decreasing prevalence of NTD. The first study was published in 1964. 1484 women under obstetric care when folic acid deficiency was quite common had been investigated. It was shown that insufficient folic acid levels resulted in congenital anomalies including NTD, megaloblastic anemia, and abruptio placentae, and emphasized that true prophylaxis should be started prior to conception in every woman.[9–11] It must be noted that folic acid is not a panacea to prevent occurrence in all cases, and that about 30% of the NTD recurrence is not folic acid-preventable which suggests that a proportion of NTD are resistant to folic acid. Fortunately, new studies pointed out another nutritional agent, myo-inositol, one of inositol isomers which is cyclic sugar alcohol obtainable from vegetables, citrus fruits, cereal grains and so forth, as a potential factor preventing spinal and cranial NTD.[12–14] Calcium formate also has been shown to have preventive effects on NTD in mice but evidence is not yet forthcoming in prevention of human NTD.[15]

Mother's age

In a meta-analysis, a correlation between maternal age and higher risk for NTD was investigated. The authors stated that mothers over 40 years old and less than 19 years have an increased risk of having a child with NTDs and the risk was greater for spina bifida than for anencephaly.[16]

Socio-economics factors

Studies on the influence of socio-economic factors indicated that mothers with higher education and higher social status are less likely to have children with NTD, but this finding may be partially explained by the fact that these mothers are more likely to use folic acid in preconception period and during the neural tube closure.[17]

Ethnic groups

Centers for Disease Control and Prevention report that spina bifida and other NTD are more common in certain ethnic groups such as the Hispanic living in America. Women of African American and Asian descent seem to have the lowest prevalence of spina bifida. However, the society of United States is increasingly multicultural and diverse, making more difficult to categorize individuals into distinct ethnic/racial group.[18]

Chemical factors

Parents with exposure to organophosphorus agents have an increased risk of having progeny with NTD. **(8?)** The correlation between maternal exposure to pesticides and neural tube defects (NTD) in offspring was evaluated in 184 Mexican women living in the USA and 225 women in a control group. If the mothers were exposured to pesticides, the risk of NTDS also increased, especially when pesticides were used in the perinatal period within 0.25 miles from home.[19] Spina bifida (SB) is a common congenital developmental defect in southeastern Mexico. Parents of children with SB reside in areas where frequent pesticide use and agricultural activities are high, suggesting potential exposure to pesticides. Paraoxonase 1 (*PON1*) is the enzyme responsible for deactivation of organophosphates in the central nervous system. Polymorphisms of *PON1* genes influence the catalytic activity and plasma protein level of the enzyme. Results suggest that *PON1* polymorphisms are relevant risk factors for having offspring affected with SB.[20] Recent studies have suggested that mothers employed in the chemical industry as cleaners or generally, which have contact with chemical substances (e.g. nursing, process-

ing food and beverages, farming, textile dye and leather industries, spraying pesticides) have a higher risk of having children with congenital defects including CNS malformations.[21–23]

Hyperthermia

Hyperthermia (HT) is a well-studied teratogenic factor that induces serious developmental defects, including NTD. Hyperthermia is defined as a temperature of at least 1.5 degrees C over normal core body temperature The teratogenicity of hyperthermia was first recognized in the laboratory during animal research (Edwards, 1966), and subsequent epidemiological and clinical studies have shown that HT is also a potential teratogen in humans.[24,25] Enhanced core body temperature appears to interfere with several critical developmental events such as cell proliferation, migration, differentiation and apoptosis. The sources of hyperthermia in humans might be febrile illnesses, sauna bathing, hot tub use and excessive physical exercise in a warm and humid environment.[26] The central nervous system is especially susceptible to damage induced by too high body temperature.[27,28] The mechanism of HT-induced NTD is not well understood. Studies have shown that hyperthermia induces apoptosis by activation of the mitochondrial apoptosis pathway, which is characterized by the release of cytochrome C and the subsequent activation of caspases, cleavage of poly ADP-ribose polymerase, DNA fragmentation and activation of the p53 protein- transcription factor called "the guardian of the genome".[29–31] Fetus exposed to hyperthermia can be born with spina bifida, encephalocele, microphthalmia, microthynthesis, external ear anomalies, heart defects, hypospadias, gastrointestinal defects, cleft lip and / or cleft palate, abdominal wall defects, diaphragmatic hernia, Hirschsprung disease, Moebius syndrome, and can also lead to spontaneous miscarriage.[32]

Taking of paracetamol in the first trimester of pregnancy for illnesses with fever does not increase the risk of serious congenital abnormalities and may reduce the risk of several developmental defects.[33]

Drugs

Various drugs interfering with metabolism of folic acid or disturbing its absorption like antiepileptic drugs (such as valproate and carbamazepine), sulfamethoxazole, trimethoprim (antimicrobials), methotrexate, azathioprine (immunosuppressant), acetylsalicylic acid (anticoagulant), sulfadoxin-pyrimethamine (anti-malaria agent), sulfasalazine (anti-ulcerative colitis), antacids, rifampicin (anti-tuberculosis) and androgenic hormones, etc. may increase NTD risk. These medicines should be avoided or used with caution especially in women of childbearing age.[34,35] Kondo et al. in 2013 performed a case-control study that revealed the use of antiepileptic drugs (AEDs) without folic acid supplementation resulted in a 20.2-fold higher risk for an affected pregnancy, compared to using no AEDs or using AEDs with folic acid supplementation.[36]

Cigarettes smoking during pregnancy

Pregnant women who smoked had significantly lower concentrations of serum folate and lower concentrations of red blood cell folate, than pregnant women who did not smoke. Lower levels of serum folate may account for the higher rate of miscarriage, stillbirth and fetal anomalies like NTD, that are observed in pregnant women who smoke.[37]

Obesity

Obesity is also a risk factor for NTD, and the effect of extreme obesity is independent of the effect of folate intake. Data shows that NTD risk increased from 1.9%, for women weighing 80 to 89 kg, to 4.0% for women weighing 110 kg or more compared to women from 50 to 59 kg. NTD risk decreases by 40% with folic acid 400 µg or more / day in women weighing less than 70 kg, but folic acid supplementation has no benefit in women with higher body weight.[38,39]

Diabetes mellitus

Diabetes mellitus in pregnant mothers is a risk factor for NTD. The relative risks for major central nervous system (NTDs) and cardiovascular system defects among infants of mothers with insulin-dependent diabetes mellitus increase. Strict metabolic control well before conception and knowledge about the risk of diabetes mellitus can significantly reduce the incidence of birth malformations among their infants. Hyperinsulinemia is also a strong risk factor for NTD.[40,41]

Epidemiological and experimental studies on NTD provide some evidence that a host of physical agents (e.g. X-irradiation, hyperthermia, stress), drugs (e.g. thalidomide, folate antagonists, and hypervitaminosis A), substance abuse (e.g. alcohol), chemical agents (e.g. organic mercury, lead), maternal infections (e.g. rubella, cytomegalovirus, *Toxoplasmo gondii*, syphilis), maternal metabolic conditions (e.g. phenylketonuria, diabetes mellitus, endemic cretinism), etc. are capable of causing congenital malformations of central nervous system structures.[42]

Vitamin A

It has been shown during experiments on animals that retinoic acid reveals teratogenic activity. Studies performed by Rothman et al. (1995) have shown that pregnant women who took daily ≥ 15 000 IU of vitamin A or less than 5000 IU, prevalence of NTD was 3% and 1.3% respectively. High vitamin A consumption during pregnancy is obviously harmful and must be avoided.[43]

Genetic Factors

Genetic abnormalities undoubtedly have an important impact in inducing neural tube defects in children. Animal studies have shown that there are as many as 100 mutant genes affecting neurulation and almost all of them have their homologs in humans. This suggests that NTD has a multifactorial genetic etiology. However, we know of no single gene which is solely responsible for NTD in humans. NTD are related to genes encoding proteins that are directly or indirectly connected with folic acid and methionine metabolism. NTD are more common in females than in males, and occurs more frequently in families where previously born children were also affected with NTD, although they do not follow a strict Mendelian pattern of inheritance. This risk is 3-5 fold higher than in the general population. One of the most common mutations associated with NTD has been identified in the 5, 10-methylenetetrahydrohydrofolate reductase (MTHFR) gene. The folate pathway enzyme, MTHFR is one of the most important factors that enables cell regulation of the intracellular concentration of methionine and homocysteine. This is associated with NTD by preventing the conversion of the homocysteine to metionine. A thermolabile variant of MTHFR 677TT, reduces enzyme activity and causes enzyme deficiency in 4-16% of the population, depending on ethnic group (the biggest proportion of MTHFR exhibited in the Japanese male, the lowest in the non-white Brazilian).[44] Polymorphism of C677T (C for cytosine, T for thymidine) in the MTHFR gene has been identified as a mutation that renders the enzyme thermolabile and makes it prone to higher temperature, decreases its activity leading to an increased serum homocysteine concentration.[45]

Prevention of neural tube defects and a summary

Undeniable evidence for the effectiveness of periconceptional folic acid supplementation in preventing the majority of NTD, as reported by the Medical Research Council (MRC) of the United Kingdom, has been available since 1991.[46] Periconceptional consumption of folic acid supplements is strongly recommended for women who have affected pregnancy or have a family history of NTD. Furthermore in 2015, the North American Teratology Society published officially recommendations for women of child-bearing age or women planning to conceive to take folic acid supplements prior to conception and the global strategic plan for the total prevention of folic acid-preventable spina bifida and folic acid-preventable anencephaly by 2024. Unfortunately, many studies show that there is still insufficient knowledge of women who are planning a pregnancy, about the role of folic acid in NTD prevention and the absolute need for supplementation.[47] A good solution is provided by governments that institute mandatory folic acid fortification of a centrally produced food (such as, but not limited to, wheat flour, corn flour or meal, rice, and maize flour or meal) to provide almost all adults with at least an additional 150 micrograms of folic acid per day. Presently, 80 countries have registration (Food fortification Initiative 2016) to mandate fortification of wheat flour with folic acid, and six countries implemented the fortification of rice with folic acid. Approximately 180,000 spina bifida and anencephaly pregnancies occur in 120 countries each year that may be preventable through mandatory folic acid fortification.[48] Data shows that folic acid fortification is highly cost-effective, saving approximately $5 billion dollars in direct costs in the United States alone over a 10-year span (1996–2006).[49]

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