

## Original Article

## RISK FACTORS FOR NEURAL TUBE DEFECTS: A STUDY AT UNIVERSITY-AFFILIATED HOSPITALS IN TEHRAN

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**Background:** Neural tube defects have a complex and imperfectly understood etiology involving both genetic and environmental factors. In this case-control study, we tried to determine the association of known risk factors for neural tube defects in patients referred to university-affiliated hospitals with neurosurgical services in the city of Tehran.

**Methods:** Risk factors were assessed in-person through interviews with infants' mothers. We found 192 neural tube defect cases. One hundred and ninety-three apparently normal babies were randomly selected from the same hospitals to serve as control cases.

**Results:** Maternal age of less than 18 years ( $P = 0.02$ ), female sex of the child ( $P = 0.01$ ), birth in spring and summer seasons ( $P = 0.001$ ), history of not using folic acid ( $P = 0.001$ ), less than 5 prenatal visits ( $P = 0.001$ ), and poverty ( $P = 0.02$ ) were the most important risk factors for neural tube defects. Logistic regression analysis of these risk factors confirmed these correlations. A negative history of consuming folic acid had the most significant statistical correlation with these malformations.

**Conclusion:** Poor quality diets were an important environmental risk factor in this study.

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**Keywords:** Neural tube defects • risk factor

## Introduction

Neural tube defects (NTDs), secondary to abnormal neural tube closure between the third and fourth weeks of gestational age, are among the most serious and common birth defects to cause infant mortality, morbidity, and disability.<sup>1</sup>

The condition produces dysfunction of many organs including the skeleton, skin, and genitourinary tract, in addition to the peripheral and central nervous systems. Hydrocephalus develops in the majority of these cases.<sup>2</sup>

Despite the considerable progress that has been made towards understanding NTDs, they remain among the most common serious birth defects, and the etiology of most cases is still unknown. It is

accepted that there is a genetic-environment interaction in the causation of NTDs.<sup>1, 3</sup> Genetic and epidemiologic studies have suggested high-risk groups,<sup>1</sup> which include those who have a past history of NTDs,<sup>4</sup> maternal age of less than 20 or more than 35,<sup>5, 6</sup> low or high parity (primipara and grand multipara),<sup>4</sup> and low socioeconomic status (SES) with gross nutritional deficiency and inadequate antenatal care.<sup>4, 7</sup> Several clinical and epidemiologic studies have reported various teratogens that produce NTDs in the offspring including radiation, maternal hyperthermia, exposure to heat and hot-tub use, hypo/or hypervitaminosis A, maternal viral infections, and drugs like anticonvulsants.<sup>1, 3</sup> Teratogens cause NTDs by acting as folic acid (FA) antagonists or inadequate FA availability to the embryo. A number of environmental agents also have been hypothesized in the etiology of NTDs, particularly dietary agents like zinc deficiency.<sup>1, 8</sup> However, none of these factors has been scientifically linked with NTDs. Certain occupations such as painting (male), agriculture (female worker), and welding

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(male) have been associated with an increased risk of NTDs in offspring.<sup>1</sup> Mildly elevated maternal plasma homocysteine levels recently have been observed in some pregnancies that resulted in NTDs and other birth defects. In the past 2 decades, research has shown mild hyperhomocysteinemia to be linked to an increased risk of premature atherosclerosis, pregnancies complicated by NTDs, early pregnancy loss, and venous thrombosis.<sup>1,9</sup>

There are racial/ethnic differences as risk factors for NTDs that may be due to differences in genetic susceptibility, cultural behaviors, diet, or other factors.<sup>5, 6, 10</sup>

In this study, we investigated some important risk factors associated with NTD at university-affiliated hospitals in Tehran.

## Materials and Methods

In this case-control study, patients with NTDs referred to university-affiliated hospitals with neurosurgical services in the city of Tehran were evaluated between the years 2000 – 2004.

Risk factors were assessed through in-person maternal interviews. Control cases were apparently normal babies randomly selected from the same hospitals.

The collected and evaluated data included: maternal age, neonatal gender, gestational age, birth weight, season of birth, history of using at least 0.4 mg FA 3 months before and/or after

conception, history of NTDs among family members, maternal drug consumption, type of NTDs, number of family members, number of prenatal visits, maternal and paternal jobs, and socioeconomic indices (including income less or around 1,500,000 Rials, home ownership, car ownership, color television ownership, and possession of a mobile phone).

Chi-square analysis and multiple logistic regression were used to assess the strength of association between sociodemographic characteristics and these malformations.

## Results

We found 192 babies with NTDs whose mothers were available for interview. One hundred and ninety-three apparently normal newborn babies and their mothers were randomly selected as control. Most of the affected patients had meningocele or myelomeningocele at the lumbosacral region.

There were not statistically significant differences between groups in primiparity ( $P = 0.95$ ), birth weight ( $P = 0.06$ ), gestational age ( $P = 0.24$ ), drug consumption during first trimester of pregnancy ( $P = 0.23$ ), or history of previous NTDs in family ( $P = 0.99$ ).

Except for 6 mothers (one in the case group and 5 in the control group) who had consumed FA before pregnancy, all the others had used it after medical consultation when they were found to be

**Table 1.** Important risk factors in the study group.

Risk factor	Case	Control	$\chi^2$	P value	95%CI	Odds ratio
Mat*** age						
>18	60	32	8.04	0.01	1.41 – 3.72	2.29
≥18	132	161				
Infant sex						
Female	147	91	8.04	0.01	2.36 – 5.67	3.66
Male	45	102				
Season						
Sp/Su*	132	96	10.2	0.001	1.47 – 3.37	2.2
Au/Wi**	60	97				
Times of prenatal visit						
≤4	165	71	8.62	0.001	6.36 – 17.33	10.50
≥5	27	122				
Use of folate						
Positive	33	141	16.13	0.001	7.99 – 21.63	13.60
Negative	159	52				
Poverty						
Positive	54	21	2.91	0.02	1.85 – 5056	3.2
Negative	138	172				
Education						
< high school	173	157	6.028	0.014	1.15 – 3.79	2.08
>high school	19	36				

Sp/Su\* = spring/summer; Au/Wi\*\* = autumn/winter; Mat\*\*\* = maternal.

**Table 2.** Logistic regression analysis of risk factors in case and control groups.

Variable	Beta	Odd ratio	95%CI		P value
			Lower	Upper	
Constant	2.4	—	—	—	0.01
Maternal age					
< 18	2.29	1.22	1/01	1.32	0.04
≥ 18	—	—	—	—	—
Infant sex					
Female	3.66	2.98	1.53	4.61	0.03
Male	—	—	—	—	—
Season					
Sp/Su	2.2	1.12	1.1	1.39	0.04
Au/Wi	—	—	—	—	—
Times of prenatal visit					
≤4	10.50	5.04	3.7	12.73	0.01
≥ 5	—	—	—	—	—
Folate consumption					
Positive	13.60	7.41	2.21	13.79	0.0001
Negative	—	—	—	—	—
Poverty					
Positive	3.2	1.92	0.64	3.644	0.001
Negative	—	—	—	—	—

Sp/Su = spring/summer; Au/Wi = autumn/winter; Dependent variable = NTD.

pregnant.

Among risk factors with significant statistical differences using Chi-square (Table 1) and logistic regression analysis (Table 2), history of not consuming FA had the most significant correlation.

## Discussion

It is important to determine the underlying etiology of the NTD. The overall prognosis and medical management of an affected individual is altered by the underlying diagnosis. Additionally, the risk for the parents and other family members of having other children affected with NTDs depends upon the etiology of the NTD. In some cases, treatment of maternal health concerns can substantially reduce the risk of another affected pregnancy.

Various studies have suggested that NTD risk is higher among families of lower SES, although other studies have failed to support this finding.<sup>4, 7, 11</sup> Lower SES mothers and young mothers with poorer diets contribute to higher NTD rates, but they may also be less likely to have NTDs diagnosed during the prenatal period possibly resulting in fewer induced terminations of NTD-affected pregnancies among mothers in these groups.<sup>3, 12</sup>

In our study, we compared the income and other indices of economic status between groups. Most of the affected cases were positioned in low SES families.

Maternal education of 13 or more years is

associated with NTDs, significantly lower than in mothers with high school and less than mothers with high school education.<sup>12</sup> Our study showed such an association between maternal education and NTD rate.

Marked seasonal trends in the birth incidence of NTDs have also been reported. Anencephaly and spina bifida tend to occur more frequently in spring conceptions.<sup>13</sup> This is especially true in areas where the risk is high; however, most American studies failed to demonstrate such variations.<sup>3</sup> In our study, most affected patients were born during spring and summer.

A number of studies have reported maternal age risk for NTDs to be highest among youngest and oldest women, while other studies have found the risk to decrease with advancing age or the reverse.<sup>5</sup> Although in our study, most of the mothers with infants having NTDs were more than 18 years, the statistical difference between case and control groups was significant. This difference could be due to lower SES of mothers in the studied cases. Nutritional deficiency due to poverty and poverty-related problems could predispose these mothers to NTDs.

Parity has also shown to influence NTD risk with risk being higher for the lowest and highest number of births or an increasing risk with increasing parity.<sup>4</sup>

NTD rates may also be higher among babies with lower birth weight and lower gestational age at delivery.<sup>14</sup> However, one study reported no relationship between NTD risk and plurality.<sup>15</sup> We

could not find any correlation between primiparity, gestational age, or birth weight of infants and the incidence of NTDs.

Higher incidence among females in certain ethnic groups and in the offspring of consanguineous marriages has suggested a genetic basis for NTDs. In our study, the odds ratio for female incidence was 3.66. This preponderance appears to be influenced by the presence of additional birth defects, geographical area, and other factors.<sup>16</sup> Potential explanations also could be due to differences between the sexes in embryonic development, susceptibility to teratogenic insult, and spontaneous abortion rates.<sup>4</sup> Family members with close relatives with an NTD are at an increased risk for NTD-affected pregnancies, and this risk is influenced by the population rate of NTDs. The recurrence risk for NTDs is approximately 3 – 4%, with the risk being slightly higher if the prior infant or fetus had anencephaly.<sup>4</sup> Only 2 (1.04%) of 192 cases in our study had positive family history of malformation.

Maternal epilepsy is associated with a 1% to 2% risk for offspring with NTDs and an overall two- to three-fold increased risk for congenital anomalies in the offspring. This risk is considered to be due to anticonvulsant use, in particular valproic acid and carbamazepine. Genetic factors leading to epilepsy may also predispose offspring to NTDs. The physician may wish to reduce the dosages of anticonvulsants, change to other anticonvulsants, or reduce the number of anticonvulsants taken for seizure control, in addition to prescribing high dose FA supplements.<sup>1, 3</sup> In our study, 5 out of 192 cases and 1 out of 193 controls used antiepileptic drugs (odds ratio: 5.124).

Women who do not obtain first trimester prenatal care have a significantly higher rate of NTDs than those who obtain prenatal care.<sup>12</sup> Although studies have consistently shown that some prenatal care is better than no prenatal care, the number of visits considered to be sufficient is still a subject of debate. The United States Public Health Sciences (USPHS) panel<sup>17</sup> recommended 7 visits by 36 weeks for uncomplicated nulliparous pregnancies, as compared to nine using the Kessner Index.<sup>18</sup> For multiparous women, the USPHS panel recommended six visits; the Kessner Index does not differ, based on parity. Past recommendations have emphasized that prenatal care should begin in the first trimester. In the

USPHS Panel report, however, a preconception visit was also proposed. This visit would provide the opportunity to treat specific preexisting conditions such as diabetes or hypertension and provide anticipatory guidance such as genetic counseling.<sup>19</sup> For example, better glucose control of diabetes in the periconceptional period may prevent some congenital malformations.<sup>20, 21</sup> Similarly, evidence suggests that folate supplementation in the first six weeks of gestation may prevent neural tube defects.<sup>22</sup> In our study, less than 5 prenatal visits had a significant correlation with NTDs.

Maternal periconceptional use of FA has been found to reduce the risk of both recurrent and occurrent NTDs.<sup>23</sup> This reduction occurs both in regions of high NTD rates and in regions of low NTD rates.<sup>24</sup> This association between NTDs and FA is supported by research that has shown that FA antagonists, such as methotrexate, valproic acid, carbamazepine, and trimethoprim may increase NTD risk. However, a study that examined co-trimoxazole, a FA antagonist, failed to find any association between the medication and NTDs.<sup>25</sup> It is not known whether FA reduces risk of NTDs associated with antiepileptic medications.<sup>26</sup> Because NTDs are induced during the first 28 days of pregnancy, adequate maternal folate intake has to start preconceptionally. How FA prevents NTDs is not exactly clear. FA is essential for the synthesis of nucleic acids and amino acids and for cell division. FA may not reduce NTD risk to the same degree in all racial/ethnic groups,<sup>27</sup> suggesting that a genetic component may be involved. One type of genetic factor that has been implicated in multifactorial NTDs is the genetic variants in enzymes used in the homocysteine metabolism cycle. In this situation, FA supplementation helps improve enzyme function.<sup>28, 29</sup>

In this study, negative history of maternal folate consumption was the most important risk factor ( $P = 0.001$ , Table 1;  $P = 0.0001$ , Table 2). With respect to lower SES of our cases, it seems that nutritional deficiency has the most important role in these patients.

Without doubt, good nutrition through a diet containing abundant fresh fruits and vegetables along with a well-balanced intake of other representative food groups goes a long way towards preventing NTDs. In all geographic regions during periods of drought, famine, and war

the rate of NTDs strikingly increases, and during periods of prosperity it declines.<sup>4, 7</sup> Because neural tube development occurs very early in pregnancy and many pregnancies are unplanned, the Centers for Disease Control (CDC) and Prevention recommends that all women capable of child-bearing regularly consume 0.4 mg of FA daily (the amount present in most multivitamins). The CDC estimates that increased FA intake could reduce the incidence of NTDs by 50%.<sup>10</sup> An attempt to increase the daily folate intake for all women of childbearing age through supplementation in the food chain has also been mandated in some countries. The objective has been to obtain an average daily dose of 0.4 mg folate.<sup>3</sup>

NTDs are among the most common congenital anomalies that we encountered. Seasonal variations, poverty, young age of the mother, and a negative history of folate consumption have all contributed to our recognition that poor quality diets are an important environmental contributor to NTDs. Fortification and supplementation of FA and prenatal screening could decrease NTDs and other devastating conditions.

Programs should be implemented to educate physicians, other health professionals, and the public about the value of FA in preventing NTDs. It should also be emphasized that not all NTDs could be prevented by FA supplementation. It is also recommended that pregnant women should be offered prenatal screening or diagnostic testing to identify fetal abnormalities.<sup>20</sup>

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