Prevalence and Correlates of Neural Tube Defect in South West Iran
Retrospective analysis

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Neural tube defects (NTDs) are among the most common defect of human congenital malformations, affecting 0.6 per 1,000 live births in the United States, where there are approximately 4,000 NTD complicated pregnancies annually. Spina bifida and anencephaly are the most commonly reported NTDs, which affect 4,000 pregnancies resulting in 2,500 to 3,000 births in the United States each year. Although its etiology remains a mystery, remarkable advances have been made in the understanding and prevention of NTDs over the past few decades.

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A number of risk factors are associated with NTDs. A previous pregnancy with an NTD has the strongest association, with a relative risk of 10. There are strong ethnic and geographical associations with NTDs.4

The most commonly cited causes for NTDs include a deficiency in folate concentrations.5, 6 Genetic susceptibility, environmental factors, in utero drug exposure, and/or abnormal metabolic pathways that lead to a failure of neural tube closure during fetal development has also been linked with NTDS.7, 8

In view of the large number of pregnancies complicated by NTDs in Khuzestan and because of the many risk factors, such as socioeconomic status, nutritional deficiency, ethnicity, consanguinity, multiparity, geography and mutagens like chemical bombing in this region, this study aims to explore retrospectively the rate and associate factors for NTDs in this particular region of Iran.

METHODS

The medical records of all pregnant women, including those with documented NTDs, who attended the Jundishapur University Hospitals, in Ahvaz, from 21 March 2002 till 20 March 2004, were reviewed.

Data regarding NTD variations, the gender of affected fetuses, maternal age, parity, any family relationship of the couple, previous affected pregnancies or wastage, and mother’s blood group and Rhesus factor (Rh) were looked for and recorded. Moreover, the results were also analytically assessed. Data were compared using Chi square test: \( \rho \)-values < 0.05 were considered statistically significant. All analyses were performed using the Statistical Package for Social Science /PC+ software (version 7). The study was approved by the Internal Review Board of the Obstetrics & Gynecology Department at Jundishapur University of Medical Sciences.

RESULTS

Among 13,262 medical records of live births, 56 women had fetuses or newborns with NTDs (4.2 per 1,000 births): anencephaly (n=30, 53.6%), spina bifida (n=15, 26.8%), meningocele (n=5, 8.9%), encephalocele (n=3, 5.4%), anencephaly plus meningo-myelocele (n=3, 5.4%).

As for the gender factor, among 56 pregnancies affected with NTD, 39 (70%) were female and 17 (30%) were male. This difference is statistically significant \( (p<0.05) \). Among the 56 women whose pregnancies were affected by NTDs, 7 (12.5%) were 10-20 years old, 39 (69.7%) 21-30 years, while 10 (17.8%) were 31-40 years old.

As far as the parity factor was concerned, among the mothers whose pregnancies were affected by NTDs, 24 (42.8%) women were primiparous and 32 (57.1%) were multiparous. There was no significant difference between the two groups \( (p=0.07) \).

As for the family relationship of the couple, 31% of women with pregnancies affected by NTDs were related to their husbands. Fifty three (94.6%) of women had NTDs for the first time in pregnancy, whereas only 3 (5.4%) women had a history of NTDs in previous pregnancies. Among 56 women with pregnancies affected by NTDs, 10 (17.8%) had a history of one previous abortion and 6 (10.7%) had had more than one abortion. In terms of blood group and Rh compatibility, the blood group B was the most represented and the blood group AB was the least in women with NTD affected pregnancies. Most of the women were Rh positive.

A final correlate of NTDs that was explored in this study is climatic condition. The data suggest that there is a temporal relationship between the frequency of NTD and prevailing hot weather. The present study unequivocally suggests that NTD is highest during the two seasons of spring and autumn and thus among births in late winter and early spring.

DISCUSSION

NTDs are thought to have multifactor etiology with environmental and genetic susceptibility, maternal age, nutritional intake, exposure to drugs and harmful material, geographic region and socioeconomic status.9

In this study, we reviewed medical records of all pregnant women with documented NTDs, who attended our university hospitals between 21 March 2002 and 20 March 2004. Among 13,262 women, 56 fetuses had NTDs (4.2 per 1000 birth). This incidence is markedly higher (2 to 4 fold) than the prevalence reported elsewhere. Worldwide, prevalence of NTDs ranges from 1.4-2 per 1,000 live births.8-10

It is important to speculate on factors contributing to the high incidence of NTD in this population. It is possible that eight years of war (1980-1987) that affected this region may have led to the area being contaminated with mutagen substances. This issue would require more systematic study.
In our study, the defect with highest frequency was anencephaly with 22.6 per 10,000 births, followed by myelomeningocele (11.3 per 10,000 births), meningocele (3.8 per 10,000 births) and encephaloceles (2.3 per 10,000 births). The rate is significantly higher than previously published studies. For example, Hendricks\textsuperscript{11} in his study of a western population found a rate of anencephaly of 6.4 per 10,000 births, spina bifida: 7.1 per 10,000 births, encephalocele: 1.1 per 10,000 births.

In 1999, Leach et al\textsuperscript{12} reported 2.6 per 1,000 births, the prevalence of anencephaly in Poland. A study from Rosch et al. in 1999 reported 1.25 per 1,000 births, the incidence of neural tube defects in Magdeburg, Germany.\textsuperscript{13} The incidence of NTDs in Oman is 1.25 per 1,000 births, according to study of Rajab et al.\textsuperscript{14}

There is some evidence to suggest that the female gender may be associated with a higher risk for NTDs.\textsuperscript{15} Two-thirds of newborns affected with NTDs are female.\textsuperscript{16} In our study, 70% of new borns affected with NTDs were female.

The effect of maternal age on risk of NTDs is generally considered to be small. When an association can be found, risk tends to be elevated in older or very young mothers.\textsuperscript{17} In our study, most women with pregnancies affected by NTDs were 21 to 30 years old. Although women aged 21-30 had more pregnancies affected by NTDs, this seems to be due to a bias in our study, because the vast majority of the cases studied were in that age group.

The effect of maternal parity on the risk of NTD is probably stronger than maternal age. Studies have shown both a modest risk in mothers of parity three or more and an increased risk in primiparous mothers.\textsuperscript{18} We found no difference in occurrence rate of NTDs between primiparous and multiparous mothers ($p=0.02$).

Most cases are the first affected child in their families, although inheritance of this trait is influenced by familial predisposition, which is due to its threshold hereditary patterns.\textsuperscript{16} In our study, most of the malformed fetuses were the first affected individuals in their big families. In about 30% of cases, parents of the child affected by NTDs had first cousin relationships, so predisposition to these defects is increased. Indeed, there is no clear inheritance pattern in a single family and the presence of more affected cases in a family shows a higher susceptibility in that particular family.

Women with a previous history of NTD birth have a 10 times increased risk for another NTD birth. However, the majority (95%) of NTD pregnancies occur in women without a previous history of NTD births.\textsuperscript{19} Thus the prevention of the first occurrence is of real public health importance.\textsuperscript{20}

The frequency of NTD is the highest during the two seasons of spring and autumn,\textsuperscript{15} so the defects are mostly seen in individuals born late in winter and early in the spring.\textsuperscript{6} In our study, the season in which NTDs prevalence is highest was spring. With respect to neural tube development in the first trimester, in our analysis most affected fetuses born occurred with mothers who became pregnant early in the summer. Obviously, the environmental temperature during summer in Khuzestan is 50 degrees centigrade, which could affect the prevalence of NTDs. As in the study made by Rajab and colleagues in the Royal Hospital of Oman in 1999, an environmental temperature of more than 48 degree centigrade was suggested to be risk factor in development of neural tube defects.\textsuperscript{14} This corroborates an animal study experiment, where pregnant mice, when exposed to high temperatures, had a high rate of NTDs.\textsuperscript{21}

**CONCLUSION**

Because of the high incidence of NTDs and especially anencephaly in Khuzestan, it is recommended to institute a nationwide educational programme and to establish public health guidelines for the prevention of neural tube defects. Over the last few decades, there has clearly been a substantial body of literature that supports the association of maternal use of multivitamins containing folic acid in early pregnancy and a reduced risk for offspring with neural tube defects. The rationale for the folate deficiency hypothesis is that prenatal supplementation with antioxidant vitamins containing folic acid decreases the incidence of birth defects, especially neural tube defects. Other preventative measures ought to be systematically explored.

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