Research Paper:

Risk Factors of Neural Tube Defects in a Sample of Iranian Population From Southern Iran: A Hospital-based Investigation

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ABSTRACT

Background and Aim: The risk factors of the Neural Tube Defects (NTD) have been previously described but there are ethnic and geographical variations. Data from the Iranian population is still scarce. The objective of the current study was to investigate the NTDs risk factors in a large sample of Iranian patients admitted to a single center.

Methods and Materials/Patients: This case-control study was performed within five years from 2012 to 2017 in Namazi Hospital of Shiraz, a tertiary referral center for neonatal anomalies in the south of Iran. One hundred newborns with NTDs were included in the study as the case group and 200 healthy newborns as the control group. We recorded the baseline characteristics including the maternal variables (age, weight, height, previous pregnancy and gravidity, gestational age), newborn information (birth weight, clinical diagnosis, clinical findings in the examination, and clinical findings in radiologic test) and medical history of the perinatal period.

Results: The baseline characteristics of the mothers were matched in both groups. NTDs were associated with lower folic acid intake during pregnancy (66% vs. 78%; P=0.030; OR 95% CI=1.82) and before pregnancy (P=0.002; OR95% CI=2.36). The prevalence of NTD was significantly higher in patients who lived in hot climates (P=0.001).

Conclusion: Taking adequate folic acid supplements before and during pregnancy can reduce the risk of NTDs in the Iranian population. Hot climate zones were associated with an increased risk of NTDs in Iran.

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Highlights

● Taking adequate folic acid supplements before and during pregnancy can reduce the risk of NTDs in the Iranian population.

● Hot climate zones were associated with an increased risk of NTDs in Iran.

Plain Language Summary

The risk factors of the Neural Tube Defects (NTD) have been previously described but there are ethnic and geographical variations. Data from the Iranian population are still scarce. In the current study, we included a total number of 100 newborns with NTDs and 200 healthy newborns. The baseline characteristics including the maternal variables (age, weight, height, previous pregnancy and gravidity, gestational age), newborn information (birth weight, clinical diagnosis, clinical findings in the examination, and clinical findings in radiologic test) and medical history of the perinatal period were recorded and compared between the two study groups. We found that NTDs were associated with lower folic acid intake during pregnancy and before pregnancy. The prevalence of NTD was significantly higher in patients who lived in hot climates. We concluded that taking adequate folic acid supplements before and during pregnancy can reduce the risk of NTDs in the Iranian population. Hot climate zones were associated with an increased risk of NTDs in Iran.

1. Introduction

Neural Tube Defects (NTD) are still a major healthcare concern especially in developing countries with an estimated annual incidence of 0.2-10 per 1000 pregnancies worldwide [1, 2]. The annual incidence of the NTDs has been reported to be 6.4 per 1000 pregnancies [3, 4]. The NTD is among the most common birth defects along with congenital heart diseases and genitourinary anomalies [5, 6]. The most common types of NTDs are spina bifida and spinal dysraphism, anencephaly, encephalocele, and anencephaly [3, 4]. The implementation of the peri-conception folic acid supplementation program resulted in reduced incidence and prevalence of NTDs worldwide [2, 7].

Although the etiology remains unclear; however, it has been demonstrated that these anomalies are multifactorial and are associated with genetic mutations (sporadic and familial), nutritional determinants, perinatal exposure to the drugs and toxins, and environmental factors such as air pollutants, radiation exposure and water contaminants [8-10]. Several genes such as the WNT signaling pathway or the Planar Cell Polarity (PCP) pathway are responsible for the development of the NTDs [10, 11]. Mutation in 5,10 methylenetetrahydrofolate reductase (MTHFR) gene has been significantly related to raising risks of NTD in infants. A specific mutation causes MTHFR enzyme function to decrease and a meta-analysis by Zhang and co-workers reported an increased chance of having an NTDs with this mutant allele [12].

Several risk factors for NTDs have been proposed through various epidemiological and population-based studies in different geographical regions and among different ethnic groups [1, 3, 4, 8-10]. Perinatal exposure to anticonvulsants, occupational exposure of the mother to radiation, heavy metals and certain chemical byproducts have been correlated with a higher risk of NTDs [13, 14]. A previous population-based study in central Iran revealed that maternal history of abortion and maternal obesity were the only risk factors associated with NTDs in the Iranian population [15]. Although mandatory folic acid supplementation has been proposed in Iran since 2004, the incidence remains still high. This study aimed at determining the risk factors of NTDs in a considerable Iranian population in southern Iran.

2. Methods and Materials/Patients

Study population

This case-control study was conducted for 5 years from September 2012 to November 2017 in Namazi Hospital, a tertiary referral center for pediatric neurological and neurosurgical disorders affiliated with Shiraz University of Medical Sciences in Iran. We consecutively included all of the patients with NTDs who were admitted to our center during the study period as a case group. The NTDs reviewed in the current study included myelomeningocele, tethered cord, encephalocele, and schizencephaly. We also included a group of healthy newborns without any congenital anomaly and medical condition as a control group with a case to control the ratio of 1:2.

The control group was recruited from the obstetric rooms of Hafez Hospital, a tertiary healthcare center of obstetrics and gynecology with the same affiliation mentioned. The controls had at least 3 normal prenatal sonographies and were found to be healthy in the clinical examination according to the attending neonatologist. The control group was selected using random sampling method utilizing the admission numbers by a computer program. We excluded those mothers whose medical charts lacked appropriate information and those whose parents were out of reach or refused to participate in the study. We have also excluded those mothers with a history of abortion in both study groups.

To diagnose all of the NTDs as well as the occult defects, all the patients and controls underwent a complete physical examination and whole spine Magnetic Resonance Imaging (MRI). Those without appropriate information/documents were excluded from the research. The study protocol was approved by the Institutional Review Board (IRB) and medical ethics committee of Shiraz University of Medical Sciences. All of the parents, in both case and control groups, provided their written informed consents before inclusion in the study.

Study protocol

All of the patients were examined by the attending pediatric neurosurgeon and the positive findings were recorded in the data collection forms. We recorded the following information:

Maternal information

The data included age, weight, height, previous pregnancy and gravidity, gestational Age, Blood Type (ABO and Rh), history of diabetes before or during pregnancy, history of hypertension before or during pregnancy, history of infertility before pregnancy, adequate use of a prescribed folic acid supplement, history of delivery of a child with a birth defect in a previous pregnancy, history of using the anti-epileptic drug before or during pregnancy, history of being a passive or active smoker, history of the previous child with congenital anomaly and history of NTDs in the family. The climate classification was based on the national geography definition which defined the hot climate as a region with a mean maximal summer temperature of 41°C and more. Adequate pre-pregnancy folate intake was defined as taking 1 mg/day folic acid from 3 months before the pregnancy to the time of conception. Taking 1 mg/day folic acid during the pregnancy was also defined as adequate folate intake during the pregnancy.

Newborn information

The information included birth weight, clinical diagnosis, clinical findings in the examination, and clinical findings on imaging and accompanied abnormalities. These data were gathered by studying the medical records of both case and control groups and making contact with their families using phone numbers available in records. The required legal permission was previously granted.

Statistical analysis

All of the data were entered into an online database and the extracts were analyzed using the statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) V. 21.0. Data are presented as Mean±SD and proportions as appropriate. The parametric variable with normal distribution was compared using the independent t-test while those without normal distribution were compared using the Mann-Whitney U-test. The proportions were compared using the chi-square test. Odds Ratios (OR) with 95% Confidence Interval (CI) were also calculated and reported. A multivariate logistic regression model was also used to compensate for the confounders. A two-sided p-value of less than 0.05 was considered statistically significant.

3. Results

Overall, we included 100 patients with NTDs and 200 healthy controls during the study period. The mean age of mothers in case and control groups were comparable (28.08±5.04 vs. 27.74±5.35; P=0.59). The mean Body Mass Index (BMI) of case and control groups were 25.53±4.71 and 25.37±4.72 (P=0.83), respectively. The gestational age of case and control mothers were 38.13±1.89 and 38.35±1.64 (P=0.48). The mean gravidity of case and control groups was 2.47±1.32 and 2.36±1.64 (P=0.04)), respectively. Only 23% of the case group was diagnosed by radiological methods before delivery. The most common NTD type was found to be myelomeningocele (83 cases; 83%) followed by the tethered cord (11%). Other types were encephalocele (5%) and schizencephaly (1%). Overall, 3% of the mothers in the case group versus 5% in the control group had gestational diabetes (P=0.55; OR 95% CI=1.70). There was no significant difference between the two study groups in

Table 1. The baseline characteristics of the 100 patients and 200 healthy controls included in the current study

Variables	Mean±SD		P
	NTDs (n=100)	Controls (n=200)	
Maternal age (years)	28.08±5.04	27.74±5.35	0.59
Maternal BMI (kg/m^2)	25.53±4.71	25.37±4.72	0.83
Gestational age (weeks)	38.13±1.89	38.35±1.64	0.48
Gravid	2.47±1.32	2.36±1.23	0.40

BMI: Body Mass Index; NTD: Neural Tube Defect

Table 2. Risk factors analysis of patients with Neural Tube Defects (NTD) compared to healthy controls

Variables		No. (%)		P	OR (95%CI)
		NTD (n=100)	Healthy Control (n=200)		
Male gender		42 (42)	90 (45)	0.28	0.45 (0.12-1.32)
Female gender		58 (58)	110 (55)	0.34	0.52 (0.18-1.11)
History of diabetes		3 (3)	10 (5)	0.55	1.70 (0.45-6.32)
History of mother infertility		4 (4)	10 (5)	0.78	1.26 (0.38-4.13)
Age more than 40 or less than 18		1 (1)	2 (1)	1.0	1.0 (0.09-11.16)
Taking adequate folic acid supplement during pregnancy		66 (66)	156 (78)	0.031	1.82 (1.07-3.10)
Taking adequate folic acid supplement before pregnancy		22 (22)	80 (40)	0.002	2.36 (1.36-4.10)
Previous infant affected by birth defect		4 (4)	2 (1)	0.09	0.24 (0.04-1.34)
Antiepileptic drugs during pregnancy		2 (2)	0 (0.0)	0.11	-
BMI more than 28		24 (24)	48 (24)	1.0	1.0 (0.57-1.75)
Low birth weight		13 (13)	20 (10)	0.43	0.74 (0.35-1.56)
Geographical region	Hot	70 (70)	85 (42.5)	<0.001	2.31 (0.23-5.34)
	Cold	16 (16)	38 (19)	-	-
	Moderate	14 (14)	77 (38.5)	-	-

the rate of infertility [4% vs. 5%; P=0.78; OR 95% CI=1.26 (0.38-4.13)]. The baseline characteristics of the patients and their controls are summarized in Table 1.

The gender distribution of the neonates was also comparable between the two study groups (P=0.34). The number of mothers who took folic acid before pregnancy was significantly higher in control than the case group [40% vs. 22%; P=0.002; OR 95% CI=2.36 (1.36-4.10)]. Moreover, taking adequate folic acid during pregnancy was significantly higher in control than case group [78% vs. 66%; P=0.03; OR 95% CI=1.82 (1.07-3.10)]. Maternal BMI≥28 kg/m^2 was comparable between the two study groups (P=1.0). The neonatal low birthweight rate was also comparable between the two groups (P=0.43). In our study, the prevalence of NTDs was significantly higher in patients who lived in a hot climate (P<0.001). The results of the univariate logistic regression are demonstrated in Table 2.

4. Discussion

NTDs are currently considered among the most important congenital anomalies associated with Central Nervous System (CNS) involvement. According to the World Health Organization, NTDs affect between 1 and 10 in every 1000 live births which vary significantly between different ethnic and geographical regions and groups [16]. NTDs arise from the improper closure of the NTD during early pregnancy. Overall, our results suggest that taking adequate folic acid before and after pregnancy contributed substantially to the prevention of NTDs.

Evidence from randomized trials and intervention studies has established that maternal consumption of folic acid before pregnancy as well as during the first month of pregnancy is associated with decreased risk of NTDs. Thus, folic acid supplementation is considered as a standard means of primary prevention of NTDs [17-

19]. In fact, in an animal model of rat, these findings have been confirmed and the acid folic supplementation is protective against the NTDs [20].

Our study showed that maternal diabetes and antiepileptic drugs are not risk factors for NTDs in the Iranian population. The reason for these findings may be related to the low sample size. Shaw et al. suggested that except for many of the febrile illnesses during pregnancy, other illnesses and medications relating to their treatment in this period, do not seem to have a fundamental effect on the occurrence of NTDs [21].

Our survey also indicated that fever and febrile illness are associated with increased risks of NTDs. We concluded that gender distribution was similar in two groups. Our results showed that the male/female ratio was 0.72 and 0.81 in case and control groups, respectively. Similar to our study, Kallen et al. reported that the sex ratio in patients with NTD was 0.74 [22]. Moreover, Deak et al. showed that the sex ratio was 0.52 in the NTDs group and 0.64 in the control group [23].

Our results suggested that the two groups were similar according to maternal BMI. In contrast to our study, Rasmussen et al. specified that maternal obesity increases the risk of NTDs [24]. Furthermore, Ray et al. confirmed the results of the previous study regarding the effects of maternal weight on the risk of NTDs [25].

The difference in the results may be due to the low sample size in our study. In this study, we found that the hot climate is a risk factor for NTDs. In contrast to our study, Soim et al. did not notice a significant relationship between climate and NTDs [26]. Wu et al. in their nested case-control study, realized that infertility could be connected to an increased risk of spinal NTDs among infants while no statistical difference was found between the two groups in our study (P=0.78) [27]. This may result from the low sample size and even fewer cases with a history of infertility [27]. Fever or increased maternal body temperature has also been linked to the increased risk of NTDs.

Several studies have addressed the association between increased body temperature and the risk of NTDs. They demonstrated that increased body temperature during the preconceptional period as well as hot climate are associated with increased risk of NTDs. However, maternal hypothermia is not associated with NTDs' risk. The mechanism of these findings is less known; however, there are some theories in the literature. The elevated body temperature during the preconceptional period will result in mitotic inhibition and subsequent genetic abnormalities in cell division. One explanation for the lack of association observed in our study may be that the core body temperature of mothers who experienced hot weather did not increase at a level that cause inhibition of the pathogenic mechanism [26].

Despite all the efforts, only 100 cases of patients with NTDs met our inclusion criteria which affected sample size and limited our results as discussed before in discussion. We faced lots of missing data in medical records in this study which led us to contact families for completing the required data. Since we contacted families for filling out the questionnaire, we also faced recall bias which also had an impact on our results.

The other limitation of the study was the selection bias. We included all the NTDs who had been admitted to the Namazi Hospital and did not include those in very deprived areas who had not been referred. However, Namazi is the referral center for all of the NTDs in southern Iran and this bias would thus be minimal.

Another limitation of the study was the role of confounders. There are several factors such as occupational exposure of the mother to radiation, heavy metals, and certain chemical by-products, and air pollutants which could not be matched and excluded in the current study. We recommend further studies to address these issues. Due to the importance and heavy burden of NTDs on public health, we would suggest further studies with a bigger sample size to prevent such biases.

5. Conclusion

In conclusion, according to the results of the current study, taking adequate folic acid supplements before and during pregnancy can reduce the rate of NTDs. The NTD incidence was also associated with the hot climate zone in our country.

Ethical Considerations

Compliance with ethical guidelines

There was no ethical considerations to be considered in this research.

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Authors contributions

Conceptualization and methodology: Mohammad Sadegh Masoudi and Negin Hadi; Data collection: Mohammadreza Askarpour, Faeze Ershadi, Tayebeh Sadeghpour; Data analysis: Fariborz Ghaffarpasand, Mohammad Sadegh Masoudi and Negin Hadi; Drafting the article: Fariborz Ghaffarpasand; Critically revising the article: Mohammad Sadegh Masoudi, Negin Hadi, Mohammadreza Askarpour; Reviewing the submitted version and approving the final version of the manuscript: All authors.

Conflict of interest

The authors declared no conflict of interest.

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