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Original Article

Neural Tube Defects in Native Fars Ethnicity in Northern Iran

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Abstract

Background: Neural tube defects (NTD) are one of the leading causes of infant mortality worldwide. This study was designed to determine the prevalence of NTDs among native Fars ethnic groups during 1998-2005, and to identify maternal and demographic factors associated with NTDs.

Methods: We performed a descriptive cross-sectional hospital-based study in Dezyani Hospital, Gorgan, North of Iran, since January 1998 until December 2005. The design was based on a sample of 30,639 births of native Fars ethnic groups**.** Data were analyzed by using spss V13.5 software and were compared with the chi-square test.

Results: The prevalence of NTDs in Native Fars during the 8-year period was 25.4 per 10000 births (95% confidence interval: 20.1-31.8). The prevalence of NTDs was 20.6/10000 and 30.6/10000 in males and females respectively but this difference was not significant. The prevalence of spina bifida, anencephaly and encephalocele were 12.7, 11.4 and 1.3 per 10000 respectively. The rate of NTD was 48.9/10000 in newborns with mothers aged > 35 years. The highest rate of NTDs and spina bifida was in 2002. The highest and lowest rate of anencephaly was in 2005 and 2003 respectively. Twenty eight percent of the parents had consanguineous marriages. Degree relatedness 3, 4, 5 and 6 of consanguineous marriages were 12.8%, 9%, 3.8%, 2.5%, respectively. Also 47.5% of the parents resided in rural areas.

Conclusion: This investigation showed that the rate of NTDs in Native Fars was higher in Iran. In addition, this rate is higher than the Canada and Ukraine and lower than Chinese people.

Keywords: *Neural tube defects, Ethnicity, Epidemiology, Iran*

Introduction

Birth defects are one of the leading causes of infant mortality worldwide. Incomplete or incorrect closure of the neural tube during early embryologic development causes neural tube defects (1-3). Miscarriage, stillbirth and disability during lifetime were outcomes of NTDs (4). The etiologies of NTDs are considered complex, and in most cases, the causes of these conditions remain elusive (5). Multifactorial disturbances in embryonic neurulation have been identified as cause of NTDs (6, 7). NTDs are caused primarily by chromosomal abnormalities, single-gene disorders, and environmental agents (8). Exposure to methotrexate, aminopterin and valporic acid, maternal characteristics, racial, ethnic, geographical, nutritional, biological factors and low socioeconomic condition have been recognized as risk factors for developing NTDs (9-12). The prevalence of NTDs in different studies; varies from 1 case in 100 in some regions of China to about 1 case in 2000 in some Scandinavian countries. Overall, the prevalence is approximately 1 in 1000 births (12-15). Previous studies have suggested that there is a racial predilection for this condition. In previous US studies, the NTDs rate varied with ethnicity (16, 17), but potential confounders, including maternal weight (18) and the presence of diabetes mellitus, (19) were not controlled (20). The incidence was highest among the Malay population, compared with the Chinese population and other races (21).

Gorgan is the capital city of Golestan Province in northern Iran, where different ethnicities such as native Fars, Turkman, and Sistani reside. The native Fars group is the predominant inhabitants of the region that included 45% of total population. Dezyani is a teaching hospital and a gynologi-

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cal referral center, which is the main site for about 80% of deliveries in Gorgan. This hospital is a referral hospital with an annual rate of more than 6000 deliveries, accounting for 20% of annual birth in Golestan Province of Iran and the largest portion of deliveries (80%) in the city.
The aim of this study was to determine the prevalence of NTDs among native Fars population and to identify maternal and demographic factors associated with NTDs in this area.

Materials and Methods

Data collection

We performed a descriptive cross-sectional hospital-based study and included all live and stillbirths newborns delivered in the Dezyani Teaching Hospital, Gorgan, from January 1998 until December 2005. This hospital is the largest referral hospital in the city with an annual rate of more than 6000 deliveries that accounts for 80% of deliveries in the city and 20% of annual births in Golestan Province. Patients are usually from moderate to low socioeconomic class families of various ethnic backgrounds.
In Golestan, the three main ethnic groups are Fars, Turkman, and Sistani. The region has a population of about 1.8 million and covers an area of about 20,460 square kilometers. NTDs were defined according to the International Classification of Diseases, Tenth Revision (ICD-10). NTDs were confirmed by a pediatrician (neonatologist). This study aims to estimate the prevalence and trends of congenital malformations in native Fars groups who had three previous generations in this area and was not Turkman, Sistani or other ethnicities and their correlation with maternal variables, and type of neural tube defect, associated malformations, prenatal diagnosis, type of consanguineous marriages and the other demographic information. The design was based on a sample of 30,639 postpartum women after admission for childbirth in maternity hospital in Gorgan, capital city of Golestan province that is a referral center for obstetrics and gynecologic problems. Data were collected through interviews with mothers in the immediate postpartum, as well as by consulting the patient records of both the mothers and newborn infants.
The data were analyzed using SPSS version 15 and STATA SE version 10 softwares and were compared with the chi-square and ANOVA test. Because of rarity of NTD, the 95% confidence interval for prevalence was estimated depends on binomial exact methods. A *P*-value of 0.05 or less was considered statistically significant. Crude and multivariate odds ratios (ORs), along with 95% confidence intervals (CIs), were derived using unconditional logistic regression analysis. All variables were included in the model a priori.

Results

Between 1998 and 2005 there were 30639 births in Native Fars in Dezyani teaching hospital, Gorgan, with 78 newborns and stillbirths recorded with NTDs. The prevalence of NTDs in Native Fars during the 8 yr period was therefore 25.4 (95% confidence interval: 20.1-31.8) per 10000 births. There were 33 males and 45 females; the rate of NTD was 20.6/10000 and 30.6/10000 in males and females respectively (χ^2= 3.0, *P*= 0.08) (Table 1).
Out of the 78 NTD cases in Native Fars, 39 spina bifida, 35 were anencephalic and 4 had encephalocele. The corresponding prevalence for spina bifida was 12.7/10000 births (10.02 and 14.4/10000 for males and females respectively) (x^2= 1.9, *P*= 0.17), for anencephaly 11.4/10000 (8.7 and 14.3/10000 for males and females) (x^2= 2.1, *P*= 0.15) and for encephalocele 1.3/10000 (1.87 and 0.68/10000 for males and females) (Fisher's Exact *P* value= 0.63).
According to mother's age; the highest rate of NTD was 48.9/10000 in newborns with mothers aged > 35 yr (Table 1). This study showed that 22(28%) of the parents with affected newborns had consanguineous marriages. degree relatedness 3, 4, 5 and 6 of consanguineous marriages were 12.8%, 9%, 3.8%, 2.5% respectively. one mother was diabetic patient and during pregnancy treated with insulin.
Also 47.5% of the parents resided in rural areas and 52.5% in urban areas.

The rate of NTD and the rate of spina bifida, anencephaly and encephalocele for each year are shown in Fig. 1. The highest rate of NTD was in the year 2002 (40/10000). In addition, the highest rate of spina bifida and encephalocele was in the year 2002. The lowest rate of NTD was in 2000. The highest and lowest rate of anencephaly was in 2005 and 2003. The trend of NTDs, spina bifida, anencephaly and encephalocele during 1998-2005 is depicted in Fig. 1.
According to the ANOVA variant test and due to TUKY test we could observe the significant difference in the prevalence of NTD in 8 yr separately (Table 2).

Table 1: Prevalence of neural tube defects (per 10 000) by sex and mother's age, 1998-2005

Variable	Total No. of births			Anencephaly No/10000		Encephalocele No/10000		Total No/10000		x^2	*P* value
Sex											
male	15962	16	10.02	14	8.7	3	1.87	33	20.6	3.0	0.083
female	14677	23	14.4	21	14.3	1	0.68	45	30.6		
Mother's age (yr)											
15-19	3677	4	10.8	6	16.3	1	2.7	11	29.9	3.25	0.20
20-34	25737	31	12.04	27	10.4	3	1.1	61	23.7		
≥ 35	1225	4	32.6	2	16.3	0	0	6	48.9		

Table 2: Differences of NTD prevalence during 8 years of study (1998-2005)

Year	Years	*P* value	95%CI (lower bound)	95%CI (upper bound)
1998	2002	0.001	-29.4	-6.57
1999	2002	0.020	-24.4	-1.57
2000	2002	0.000	-32.7	-9.87
	2005	0.008	-26.1	-3.27
2001	2002	0.003	-27.8	-4.97
2002	1998	0.001	6.57	29.42
	1999	0.020	1.57	24.42
	2000	0.000	9.87	32.72
	2001	0.003	4.97	27.82
	2003	0.000	8.94	31.79
	2004	0.001	7.32	32.87
2003	2002	0.000	-31.7	-8.94
	2005	0.013	-25.1	-2.34
2004	2002	0.001	-32.8	-7.32
	2005	0.035	-26.2	-0.72
2005	2000	0.008	3.27	26.1
	2003	0.013	2.34	25.1
	2004	0.035	0.72	26.2

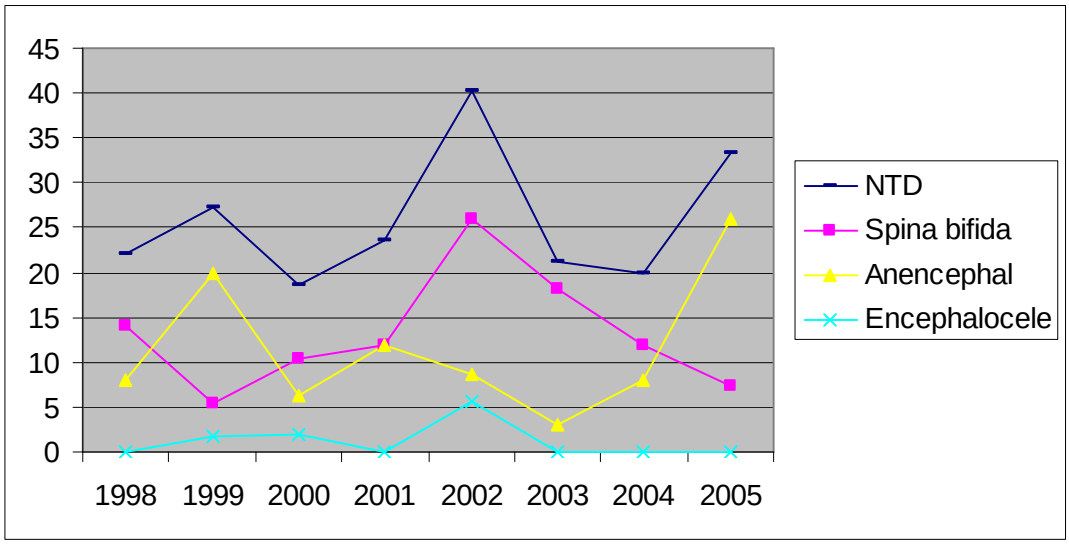

Fig. 1: Annual rates of neural tube defects and its classification (/10 000 births)

Discussion

The overall NTD rate in native Fars ethnicity for the period of 8 yr study period was found to be 25.4 /10 000 births, which this finding is nearly in agreement with previous report. Our previous report showed that the rate of NTDs in native Fars group during 1998-2000 was 23.5/10 000 births but in total population in Gorgan region the rate was 31/10 000 births. Furthermore the rate of NTDs in this study is more than reports from other parts of world with various races/ethnicities including Canada with 1.41/1000 (15) and 3.9/1,000 in 2002 (22), Cape Town 1.74-0.63/ 1,000, 20 yr period (23), United States of America (USA) 9.3 to 14.6/10 000 (12), South Africa 1.74/1000 (24), Southern Africa (1.3/1 000)1980-1984, (25) southern Nigeria 0.95/1000 (26), Northwestern Ukraine 2.1/1000 (2000-2002) (27), Germany 15.0/10 000 (28), the north of England 17.9/10 000 (29) and north of France 10.9/10 000 (30). It is also higher than the capital city of Iran "Tehran" where it was 17.6/10000 (31) (1969-78). The rate is lower than the rate of north-west of Iran (Hamadan) 50.1/10 000 (32) and Kordestan 55.0/10000 (33). This rate was also lower than the other countries such as in rural Transkei district of Umzimkulu which was 3.79 /1000(25), in China 6.0/1000 (34), in Shanxi province of China 199.38/10 000 (4), in Turkey 30.1/10 000 (10), in South Carolina 10.29/10 000 (1992-1996) (4, 35) and in Cameron County, Texas (USA) 27 /10,000 (1990-1991) (36).

These variations in different studies could be explained by the influence of racial and social factors in various parts of the world, which are commonly explained as genetic disorders. Geographical, nutritional, socioeconomic, and biological factors could also be involved. Other reasons for these variations in birth defect prevalence are the type of sample (referral hospitals would be expected to have higher rates) and method of diagnosis. Spina bifida was the most common NTD in our study, which agrees with other studies (37, 38), followed by anencephaly and encephalocele. The rate of cystic spina bifida in our study population was 12.7/10 000, which is higher than 6.2/10 000 in France (39), 5.5/10 000 in Atlanta (40), 7.1/10 000 in Texas (12), 1.09/ 10 000 in Saudi Arabia (41), 3.8/10 000 in Tehran (capital of Islamic Republic of Iran) (31) and in Hamadan (north-west province) with 6.98/10 000 (32). The rate of anencephaly in our study was 11.4/10 000, which is higher than the other studies such as 6.0/10 000 in South America (42), 3.7/10 000 in Atlanta (40), 6.4/10 000 in Texas (12) and 8.0/10 000 in Tehran (31). However,

the rate in our study was lower than in Hamedan with 15.6/ 10 000, China with 87.0/10 000 and Turkey with 16.4/10 000 (32). The rate of encephalocele (1.3/10 000) that was nearly similar to studies in the USA (1.03/10 000) (12) and Atlanta (1.4/10 000) (40). However, encephaloceles were significantly more common among the offspring of Hispanic women (adjusted prevalence ratio: 1.91) 1999-2002 (5).

Previous studies reported that the rate and distributions of many of the birth defects such as NTDs related to the sex (4). Regarding sex differences, our results indicate that the rate of NTD was higher in females than males (male to female ratio= 0.73), as reported by other researchers (4, 12, 23, 25, 35, 43, 44). The male to female ratio was 0.66 for anencephaly and 0.69 for spina bifida, which is also comparable to other studies (4, 12, 23, 31, 35, 39, 41, 42, 45). For example, in the USA the ratio for all NTD was 0.62, for anencephaly 0.54 and for spina bifida 0.68 (12). Our research showed that the highest rate of affected newborns was in mothers aged ≥ 35 yr (48.9/10 000), with 29.9/10 000 in mothers aged 15-19 yr and 23.7/10 000 aged 20-34 yr. Our study showed a U-shaped curve with higher rates in mothers aged under 19/20 yr and over 35 yr (12, 23, 24, 39, 46, 47) which was in contrast with other studies (4, 5, 35). Thus, age is a complex risk factor in NTD and this issue needs more investigation. Some researches have shown that the rate of consanguineous marriage is high in NTD births (38, 41). In our study, 28% of parents with affected newborns had consanguineous marriage, although this rate is lower than in Saudi Arabia (89% of the spina bifida parents) (41) and higher than in South Africa (24). In addition, a report from North-west of Iran showed that 23% of parents with healthy infants had familial marriages (48) .The possibility that consanguinity could be a risk factor for NTD in a population requires further research. In this study, 47.5% and 52.5% of parents with affected newborns lived in rural and urban areas respectively. A greater prevalence of NTDs at birth has been shown for rural areas compared with urban areas (49, 50). A report from China (1988–1991) indicated the prevalence of NTD in rural areas (44.3/10 000) was 3 times higher than urban areas (14.4/10 000) (51). It may be due to factors such as high population growth rates and socioeconomic factors. In our study the highest rate was seen in the year 2002 (40/ 10000), but in Quebec city of Canada, the average NTD prevalence decreased from 12.2/1,000 in 1993 to 3.9/1,000 in 2002 (22). In our study the relation between prevalence and year is seen in Fig. 1, the highest rate is seen in 1999, 2002 and 2005 which is due to immigration, socioeconomic, agriculture condition or nutritional factors (52).

According to our findings, interfamilial marriage may play a role in the NTD rate in this region of the Islamic Republic of Iran, although there could also be effects of environmental and nutritional factors. In this research, we could not study abortions and therefore our results may be underestimated.

In conclusion, the present study confirmed the previous reports of high prevalence of NTDs in this region (53). This approach has the advantage of capturing all essential information necessary for an accurate evaluation of NTDs prevalence in our region, and is applicable for other studies estimating the prevalence of birth defects. These findings will help establish a database for future studies, which will focus on multiplex causes and preventive factors to reduce the prevalence of NTD in this region.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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