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NEURAL TUBE DEFECTS IN TURKEY: PREVALENCE, DISTRIBUTION AND RISK FACTORS*

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The aim of the study was to determine the prevalence rate and risk factors relevant to neural tube defects (NTDs) in Turkey. All livebirths and stillbirths recorded at the university hospitals throughout Turkey between July 1993-June 1994 were evaluated with respect to congenital anomalies. For each birth, information was recorded about the child, the mother, the pregnancy and risk factors. A total of 66 cases with a NTD were recorded in 21,907 births. Prevalence rate of NTDs was 30.1 per 10,000 births. Of these 66 cases, 29 (43.9%) were male and 37 (56.1%) female. Female/male ratio was 1.27. The ratio of spina bifida/anencephaly is 1.20 for Turkey. Maternal illiteracy, maternal advanced age and residence in northern or eastern regions of Turkey are shown to be risk factors for having a baby with a NTD. The prevalence rate of NTDs is very high for Turkey. Geographical distribution of NTDs in this country confirms a relationship between the socioeconomic status and environmental factors for the development of a NTD. The results of this study point to the importance establishing a health policy to prevent neural tube defects in Turkey. *Key words: neural tube defects, prevalence, risk factors, Turkey.*

Neural tube defects (NTDs) are one of the most severe of all congenital anomalies. Epidemiological data have shown that NTDs have regional variations in prevalence rate[1]. Unfortunately, Turkey is one of the countries for which data about the prevalence of this severe congenital malformation is missing. Since there is no registry system for births in Turkey, and only 60 percent of all births occur at a health center[2], registration of congenital anomalies has not been possible thus far.

As a part of a program to register congenital anomalies in Turkey (The Turkish Congenital Malformatilon Survey)[3] 66 cases of NTDs were recorded among 21,907 births between July 1993-June 1994. Regional variation in the prevalence rates and risk factors of NTD have been evaluated.

Material and Methods

The study began on 1 July 1993. During the preceding two months, a pilot study was done to assess the suitability and clarity of the questionnaire and ability of interviewers to collect accurate information from the mothers. This pilot study

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showed that the interviewers at Hacettepe University could ensure accurate recording of data on the questionnaire. Consequently, one interviewer from each center was invited to the registry center for a one-day course on presenting the questionnaire, including criteria for exclusion from the study group. The query form was prepared to obtain data on the following topics: a) social and cultural status of the mother, b) history and outcomes of previous pregnancies, c) history of the current pregnancy, d) family history and, e) product of the current pregnancy. The interviewer at each center was the pediatrician who had been trained at the course previously. Records for each case were transmitted on a standard form to the registry center at Hacettepe University for processing.

All births in obstetrics and gynecology departments at all (22) university hospitals in Turkey between 1 July 1993-31 June 1994 were recorded. Each hospital was from one of five geographical regions (north, east, south, west and central) of Turkey. Distribution of cases by geographical region was made on the basis of the mother's residence, not according to the region in which the hospital of birth was located. Thus, this study was a hospital-based study analyzed according to mothers residence.

Stillbirths and abortions weighing less than 500 g or of less than 20 weeks of gestational age were excluded. Each newborn was examined by a pediatrician for identification of birth defects. A routine physical examination was also performed with weight, height and head circumference measurements obtained for all newborns. All participating registries used the common coding system of the 10th revision of the International Classification of Diseases (ICD-10)[4] for definition of congenital anomalies. Malformations were classified by the organ systems according to the ICD-10.

Neural tube defects include anencephaly, encephalocele and spina bifida. The spina bifida group did not include spina bifida occulta or cases associated with anencephaly or encephalocele. Cases with the syndromic forms of NTDs, such as Meckel-Gruber syndrome, were also excluded.

Results

We observed that 84 percent of mothers in the study population were between 20-35 years of age, 50 percent graduated from secondary school or had a higher level of education, and 98 percent married after the age of 20. All these parameters show these mothers with a better social and cultural situation in comparison to the general Turkish population. However, estimated values of the infant mortality rate (89.6 per 1,000), childmortality rate (27.5 per 1,000) and under-five mortality rate (114.6 per 1,000) using preceding birth history demonstrate significantly higher rates for these mothers when compared with the rates of the Turkish population, which are 53, 9, and 61 per 1,000, respectively[2].

A total of 21,907 livebirths and stillbirths were examined, and 66 cases with neural tube defects were recorded. Prevalence rate of NTDs was 30.1 per 10,000 births. Of these 66 cases, 29 (43.9%) were male and 37 (56.1%) female. Female/male ratio was 1.27 for NTDs, 1.5 for anencephaly and 0.81 for spina bifida.

Distribution of the different types of NTDs was as follows: 29 (43.9%) cases with spina bifida, 24 (36.4%) cases with anencephaly and 13 (19.7 percent) cases with encephalocele. The ratio of spina bifida/anencephaly is 1.20 for Turkey, as it is in countries where the prevalence rate of NTDs is very high. Distribution of NTDs by geographical region is shown in Table I. Prevalence rate of NTD was higher in northern and eastern regions of Turkey, with the western region having the lowest prevalence rate. A Z-test was performed for all possible pairs. Differences between geographical regions were found to be significant when p value was < 0.01, except for the difference between prevalence rates for the northern and eastern regions, which was found to be statistically insignificant.

Table I: Distribution of NTDs in Turkey by Geographical Region

Region	Anencephaly	Spina Bifida	Encephalocele	NTD Total	Number of Cases Examined	Prevalence Rate (per 10,000) of NTDs
North	1	2	1	4	926	43.2
East	6	9	4	19	4179	45.4
South	1	2	2	5	1908	26.2
West	6	6	0	12	5523	21.7
Central	10	10	6	26	8141	31.9
Total	24	29	13	66	20677*	

* Data about the residence of the mother was not available for 1,230 cases.

Children born to mothers with a lower educational level are more likely to have NTDs than children of mothers with a higher education. Distribution of NTDs by maternal education is shown in Table II. Differences between all maternal education levels were found to be significant when p value was < 0.01 (Z-test). A child of an illiterate mother has a seven-times higher risk of having a NTD than a child of a mother with a high school education. The number of cases not completing primary school was small, which may explain the rather low prevalence rate in that group. When this group is excluded from the results, a steady decline is observed in the prevalence rate from the illiterate group to the high school graduate group.

None of the mothers of the NTD cases were older than 39. Below this age, increased maternal age is associated with a higher risk of having a child with a NTD. Distribution of NTDs is shown in Table III. Differences between all maternal age groups were found to be significant when p value was < 0.01 (Z-test).

Table II: Distribution of NTDs in Turkey by Maternal Education Geographical Region

Education of Mother	Anencephaly	Spina Bifida	Encephalocele	NTD Total	Number of Cases Examined	Prevalence Rate (per 10,000) of NTDs
Illiterate	5	5	1	11	1208	91.05
Primary incomplete	0	1	0	1	447	22.37
Primary graduate	13	10	6	29	8477	34.21
Secondary graduate	2	9	3	14	7393	18.92
High school graduate	2	1	2	5	3835	13.03
Total	22	26	12	60*	21360*	

* Data about maternal education was not available for 547 cases and 6 NTD patients.

Table III: Distribution of NTDs in Turkey by Maternal Age

Maternal Age	Anencephaly	Spina Bifida	Encephalocele	NTD Total	Number of Cases Examined	Prevalence Rate (per 10,000) of NTDs
19	0	2	0	2	1424	14.04
20-24	8	6	4	18	6623	27.17
25-29	9	11	4	24	7309	32.83
30-34	2	6	5	13	4373	29.27
35-39	5	4	0	9	1588	56.67
40-44	0	0	0	0	291	
45-49	0	0	0	0	30	
Total	24	29	13	66	21638*	

* Data about maternal age was not available for 269 cases.

Discussion

A few reports concerning neural tube defects have been published previously from Turkey[5-8]. All of them covered a population defined by the place of birth (hospital-based) and found a high prevalence of NTDs in their region. In some of these studies, assessment of the effects of the Chernobyl accident indicated a significant increase in the prevalence rate of NTDs after May 1986[5,6], whereas some others denied an increase due to this event[7,8].

The present study is also a hospital-based one, but it covers all five geographical regions of Turkey. Results of this study cannot really be compared with the previous Turkish studies because of the different methods used, but the study does provide a chance for comparison between the regions.

Evaluation of the mothers in the study population demonstrated a better social and cultural situation than found in the general Turkish population[2]. This might lead to a bias, and an estimation of a incorrect low prevalence rate of NTDs, since it is recognized that environmental factors related to poor social and cultural status impact the occurrence of this anomaly[9]. However, these women also had

higher infant, child and under-five mortality rates than Turkish women in the general population, causing them to choose university hospitals for prenatal care and delivery of their baby. Higher mortality rates estimated with the preceding birth history for the mothers in the study reveal a high risk population for congenital anomalies, again leading to a bias, although in the opposite direction. We assumed that the biases in opposite directions would minimize the deviating effect of both.

Induced abortions after prenatal diagnosis were not registered in this study. The rate of prenatal diagnosis might vary between different geographic populations, leading to a bias in the calculation of prevalence rates in different regions when livebirths and stillbirths are registered alone. However, prenatal diagnostic services were not in routine use in any regions of Turkey in 1993. Thus, we assumed that the lack of registration of induced abortions did not result in a difference of prevalence rates of NTDs between geographical regions.

When compared with the EUROCAT registries[10], Turkey has a very high prevalence rate of NTDs. Within Europe, contrasts in the epidemiology of NTDs are observed. The prevalence was much higher in the British Isles than in continental Europe in the early 1980's[1,10]. Periconceptional use of folic acid by women of childbearing age lowered the prevalence of NTDs significantly in England and Ireland[1]. The trend in the prevalence rate of NTDs confirms the impact of environmental factors, especially folic acid, on the etiology of neural tube defects. In Turkey, prevalence of NTDs is found to be very high when compared even with rates in the British Isles in the 1980's. The spina bifida/anencephaly ratio is low due to an increase of anencephaly cases when the prevalence rate of total NTDs is high in a geographical region[11]. An inverse relationship between the male preponderance and the prevalence of NTDs has also been suggested in different ethnic groups[11]. In this study, the spina bifida/anencephaly ratio was 1.20, very low when compared with the ratio (1.41) of 16 EUROCAT registries for 1990-1994[10]. The average male preponderance is 44 percent for all NTD cases, 33.3 percent for anencephaly cases and 55 percent for spina bifida cases. Consistency of our results with those of the EUROCAT study, particularly with the centers where the NTD prevalence is high, confirms the accuracy of this study. Each of the biases presumed to have effects on the results of this study is more likely to have a lowering impact on the prevalence rate of NTDs.

Recent studies have shown that periconceptional folic acid supplementation reduces a woman's risk of having a baby with neural tube defects[12]. It has been demonstrated that mothers of infants with a NTD have increased homocysteine levels[13,14]. Persons with a thermolabile form of the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) have reduced enzyme activity and increased plasma homocysteine which can be lowered by supplemental folic acid[15]. Thermolability of the enzyme has recently been shown to be caused by a common mutation (677C→T) in the MTHFR gene[15,16]. This is the first mutation shown in the etiology of NTDs.

One explanation for the high prevalence rate of NTDs in Turkey might be the high frequency of the mutated allele in the Turkish population. But, our recent studies on the role of the 677C→T mutation in the 5, 10 MTHFR gene did not show an increased frequency of the TT genotype in NTD cases when compared with the control group[17,18]. Variation in the distribution of NTDs by regions indicates contributing environmental factors.

Maternal illiteracy, maternal advanced age and residence in northern or eastern regions of Turkey are shown to be risk factors for having a baby with a NTD. Women living in western Anatolia who graduated from a high school or university and are below 35 years of age are less likely to have an offspring with a NTD. Lower socioeconomic status may correlate with a lesser consumption of folic acid and other environmental factors. We believe that this explanation for the high frequency of NTDs in Turkey is more likely. The eastern Anatolian region actually has the worst social, cultural and economic situation among the five geographic regions of Turkey[2]. The western region is the best. The geographical distribution of NTDs in Turkey confirms a relationship between the socioeconomic status and environmental factors for development of the NTD. The results of this study point to the importance of establishing a health policy in at least in two steps to avoid neural tube defects. First, establish a system to supply women of childbearing age with a 0.4 mg daily supplement of folic acid. Second, achieve use of prenatal diagnostic procedures nationwide for early diagnosis of NTDs in order to have the chance of managing the pregnancy properly. The trend in the prevalence rate of NTDs after establishment of this policy may indicate the need to discriminate between other environmental factors in Turkey.

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