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Registries of cases with neural tube defects in Denizli, Turkey, 2004-2010

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ABSTRACT. Neural tube defects (NTD) are among the most common congenital abnormalities, with an incidence of 3 per 1000 live births in Turkey. In a study of major congenital abnormalities in the city of Denizli, Turkey, abnormalities of the central nervous system are particularly common (31.1%). The objective of this study was to develop a registry of cases with NTDs in Denizli. Cases that had been diagnosed with NTD between January 2004 and September 2010 in State Hospitals of Central Denizli were retrospectively examined. The diagnoses were established based on the ICD-10 criteria. A total of 250 subjects with NTD were identified, including 123 (49.2%) females and 127 (50.8%) males with a mean age of 13.72 ± 15.62 years (age range 1-81 years). Interestingly, spina bifida constituted a significant percentage of the cases (149 cases; 59.6%). In addition, 10 (4.0%) cases had hydrocephalus plus spina bifida. The second most common diagnosis was microcephaly, which included 70 cases (28.0%). Encephalocele was observed in only 2 cases (0.8%). Development of NTD is influenced by nutrition, socioeconomic factors, and the use

of folic acid during the peri-conceptional period. Studies examining the effect of these factors on NTD in Turkey and a review of primary prevention measures are necessary.

Key words: Folic acid; Neural tube defect; Registry; Spina bifida; Turkey

INTRODUCTION

Neural tube defects (NTD) are among the most common congenital abnormalities and are a major cause of infantile and childhood deaths (Tolmie, 1996; Cengiz et al., 2004; Medveczky and Puho, 2004). The most common forms of NTD include anencephaly and spina bifida. Anencephaly is a congenital defect resulting from impaired closure of the top of the neural tube; these infants die shortly after birth (Tinkle and Sterling, 1997; Reeder et al., 1997).

Loss of the *Sox2* gene was the most frequently observed genetic abnormality in subjects with NTDs (16%). Although Nanog3 upregulation is observed in 48%, Oct4 and Sox2 in 40% of the patients, the differences were not significant, only null mutation was significantly correlated with NTD (Saxena et al., 2013). The most common maternal risk factors associated with NTDs in infants include folic acid deficiency, overweight, diabetes, drugs, consanguinity, and single-nucleotide polymorphisms (Kondo et al., 2009; Herrmann and Obeid, 2011; Carter et al., 2011). The prevalence of NTDs at birth varies significantly by national geographical strata, ethnicity, and racial groups. Worldwide, 250,000 NTDs are diagnosed annually during pregnancy (Wald et al., 2001). The frequency of NTD has been reported to be 0.1% in Europe and 0.2% in the USA (American Academy of Pediatrics, 1993; Friel et al., 1995). The incidence of spina bifida and anencephaly in 10,000 live births is 0.9 in Canada, 7.7 in the United Arab Emirates, 0.7 in France, and 11.7 in South America (Tolmie, 1996). This rate is 1 in 100 in some parts of China and 1 or less in 5000 births in Scandinavian countries (Botto and Yang, 2000).

NTDs are among the most severe congenital abnormalities in Turkey; epidemiological findings indicate that prevalence rates vary with regional and demographic features. However, this information is currently not available in the Turkish medical registry system (Tunçbilek, 2004); according to data obtained from various cities of Turkey (Akar et al., 1989; Mocan et al., 1992; Posaci et al., 1992; Güvenc et al., 1993; Himmetoğlu et al., 1996; Tunçbilek et al., 1999), the prevalence of NTD ranges from 3-5.8 per 1000 births (Tunçbilek, 2004). Rates as high as 8.9 in Izmir and 20.0 per 1000 births in Mustafa Kemal Pasa of Bursa have been recorded following the Chernobyl disaster (Hoffmann, 2001). A university clinical study demonstrated that the frequency of NTD is highest in Northern and Eastern Anatolia, with an incidence of 4.32 and 4.54 per 1000 live births, and is lowest in Western Anatolia, with an incidence of 2.17 per 1000 live births. This rate was 9.1 per 1000 live births in uneducated mothers who were evaluated based on maternal education level (Tunçbilek, 2004). A study by Bati et al. (2007) revealed that the incidence of NTD was 1.5 in 1000 births in all hospitals in Izmir. In Afyonkarahisar, the incidence of NTD was found to be 3.58 in 1000 live births (Onrat et al., 2009). Abnormalities of the central nervous system rank highest among studies investigating the registries of major congenital abnormalities in Denizli (31.1%) (Tomatir et al., 2009). The objective of this study was to identify NTD cases in registries of Denizli, highlight the disease incidence, and suggest appropriate measure that may be taken in Turkey.

MATERIAL AND METHODS

This descriptive and retrospective study on NTD survival was performed in two hospitals (Servergazi and Denizli State Hospitals) in Denizli, Turkey between January 2004 and September 2010. NTDs were defined according to the ICD-10 criteria. Data were analyzed using the Statistical Package for the Social Sciences, v. 10 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented as frequencies and percentages.

RESULTS

Totally 250 NTD cases were identified in the registries of Denizli State Hospital in 52.3% and Servergazi State Hospital in 47.7% from September 1-30, 2010. There were 123 females (49.2%) and 127 males (50.8%), with a mean age of 13.72 ± 15.62 years (range, 1-81). A total of 149 spina bifida cases (59.6%), and 10 cases with spina bifida plus hydrocephalus (4.0%) were identified. Seventy cases had been diagnosed with microcephaly (28.0%) and 2 with encephalocele (0.8%). Other less frequent findings are presented in Table 1. Approximately half of the NTDs (44.8%) were under the age of 5 years (Table 2).

Table 1. Distribution of NTD types by gender.

NTDs	ICD-10 code	N	(%)	Gender			
				Female		Male	
				N	(%)	N	(%)
Spina bifida	Q05	149	(59.6)	67	(54.5)	82	(64.6)
Microcephaly	Q02	70	(28.0)	37	(30.1)	33	(26.0)
Spina bifida and hydrocephaly	Q05.2	10	(4.0)	8	(3.5)	2	(1.6)
NTD and other anomalies	Q06	11	(4.4)	7	(2.7)	4	(3.1)
Other cerebral anomalies	Q04	7	(2.8)	4	(1.6)	3	(2.4)
Encephalocele	Q01	2	(0.8)	-	(0.0)	2	(1.6)
Malformation of aquaductus silvii	Q03.0	1	(0.4)	-	(0.0)	1	(0.8)
Total		250	(100.0)	123	(49.2)	127	(50.8)

NTDs = neural tube defects; N = number of cases.

Table 2. Distribution of neural tube defects (NTDs) by age.

Age (years)	N	%
0-5	112	44.8
6-10	23	9.2
11-15	27	10.8
16-20	24	9.6
21-25	17	6.8
26-30	10	4.0
31-35	11	4.4
36-40	8	3.2
41-45	5	2.0
46-50	6	2.4
51-55	1	0.4
56-60	0	0.0
61-65	2	0.8
66-70	3	1.2
>71	1	0.4
Total	250	100

DISCUSSION

The European Registration of Congenital Abnormalities and Twins (EUROCAT) reported a significantly higher prevalence of NTDs in most European countries compared to countries with micronutrient fortification programs (www.eurocat-network.eu). The mean rate of NTD in the EUROCAT was 7.88 per 10,000 births from 2004-2008 (Herrmann and Obeid, 2011; Khoshnood et al., 2011). The incidence of NTD in Turkey is even greater than that in Europe and the USA. Also Tunçbilek et al. (1999) reported that the rate of NTD is 1.20 in Turkey. In another study in Turkey, 100 (1.2%) of 8408 infants admitted to the neonatal intensive care unit were diagnosed with NTD during the study period. Prenatal diagnosis was made in 72% of cases, but the parents chose to continue the pregnancy. The most frequent type and site of NTD was meningomyelocele (82%) of the lumbosacral region (36%) (Aygün et al., 2013).

In this study, spina bifida was the most frequently observed condition (149 cases; 59.6%), followed by microcephaly (70 cases; 2.0%). In addition, 10 cases (4.0%) were determined to have hydrocephaly plus spina bifida. Encephalocele was found in only 2 cases (0.8%). In a similar study, Rankin et al. (2000) reported a total of 984 NTD cases, including 403 (43.1%) cases of anencephaly, 472 (50.5%) spina bifida, and 59 (6.3%) encephalocele. Zlotogora et al. (2002) reported 401 NTD cases (167 cases of anencephaly, 167 cases of spina bifida, 48 cases of encephalocele, and 19 cases with other malformations) between the years 1999-2000. Twenty-three pregnancies were affected by anencephaly, 3 with spina bifida, and 1 with encephalocele. The anencephaly rate was 8.4 per 10,000 live births [95% confidence interval (CI) = 4.5-12.0], compared with a national estimate of 2.1 per 10,000 live births (CI = 1.9-2.2). In contrast, the rate of spina bifida was 1.3 per 10,000 live births (CI = 0.3-3.8), compared with 3.5 per 10,000 live births nationally (CI = 3.3-3.7) (Centers for Disease Control and Prevention, 2013).

Environmental factors are well known to affect the etiology of neural tube defects (Rankin et al., 2000). Women who smoked during pregnancy showed a mildly elevated risk [odds ratio (OR) =1.03, 95%CI = 0.80-1.33] of having infants with NTDs (Wang et al., 2014). The geographical distribution of NTDs in Turkey indicates a relationship between the development of NTDs and socioeconomic and environmental factors. Although some polymorphisms leading to genetic effects have been demonstrated in studies worldwide (Botto and Yang, 2000; Pangilinan et al., 2010; Carter et al., 2011), the specific genes and genetic factors involved have yet to be determined. A 677C→T mutation in the methylenetetrahydrofolate reductase gene, which is thought to cause NTDs, is not a risk factor in the Turkish population (Boduroğlu et al., 1999). The large differences observed in the incidence of NTD according to maternal education, age, and socio-economic factors have suggested that in addition to potential genetic factors, various environmental factors, such as nutrition, play major roles in disease incidence. Studies examining the causative role of folic acid deficiency in NTD in different countries have demonstrated that improvement in maternal folic acid levels prevented NTD recurrence and decreased NTD incidence (Tunçbilek, 2004).

Folates and vitamin B12 play fundamental roles in central nervous system function at all ages, particularly in purine, thymidine, nucleotide, and DNA synthesis, as well as genomic and nongenomic methylation, and therefore in tissue growth, differentiation, and repair (Reynolds, 2014). The mandatory fortification of staple foods rich in folic acid to prevent NTDs began in the USA in 1998. Since then, more than 50 countries worldwide have implemented similar programs (Herrmann and Obeid, 2011). Peri-conceptional use of folic acid in women of child-bearing potential has significantly decreased the incidence of NTD in England and

Ireland (Rankin et al., 2000). A study performed in Ontario, Canada found that the prevalence of NTDs decreased from 1.13 to 0.58 per 1000 births in women following fortification with food with an additional 0.2 mg folic acid content (Ray et al., 2002). A rate of 54% was reported in another study performed in a different region of Canada (Nova Scotia) (Persad et al., 2002). Another study performed in Canada found that fortification of foods led to a 100-µg increase in daily folic acid intake in adults. However, the 400 µg daily folic acid requirement is not being met (French et al., 2003). Replacement with folic acid tablets in addition to fortification of foods appears to be the most effective method for meeting this need. Various studies performed in these countries demonstrated that the rate of use of folic acid tablets remains at 30% because of factors such as lack of information, cost, and dislike of the tablet (Tunçbilek, 2004).

Most infants with NTDs die in the first year after birth. In this study, approximately half of the NTDs were less than 5 years old. Aygün et al. (2013) reported that in 80% of the babies, the NTD sac was closed within the first 72 h of life. The most frequently observed postoperative complications included wound infection and septicemia. The mortality rate of infants with NTD during the follow-up period was 7%, and all deaths occurred in the first year of life. Sixty-two percent of the patients were found to have neurological deficits upon follow-up. Patients were re-hospitalized during the follow-up period an average of 2.9 times.

These results indicate the important role of health care providers in informing the public and patients. In addition, the role of mass media should not be disregarded and should be used effectively.

Strengths and limitations

Data were obtained from 3 different registry systems. The data was entered into the system by specialist physicians. Only NTD cases that had survived after birth could be reached for participation in this survey. No information regarding concomitant syndromes was provided. Information regarding the mother or family could not be obtained. Thus, these data do not include infants that have not yet been born or terminated pregnancies. Therefore, prevalence has not been provided in this study since it does not conform to other national data. Better registry systems for compiling national data should be developed. Information regarding prenatal screening, prenatal diagnosis, results of pregnancy screening, and family considerations should be included in the registry forms.

CONCLUSIONS

New education methods should be developed in addition to fortification of food rich in folic acid and supplementation with folic acid tablets to decrease the high incidence of NTDs. New strategies should be determined by the Ministry of Health as well as by universities, non-governmental organizations, and related institutions. Further studies should be performed to determine the differences in the incidence and distribution of NTD as well as etiological and genetic factors in Turkey. In addition, a better national registry system should be developed.

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