The incidence and risk factors of neural tube defects in İzmir, Turkey: a nested case-control study

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The aim of this study was to determine the incidence of neural tube defects (NTDs) in İzmir, Turkey, and to evaluate risk factors that may be associated with NTD-affected pregnancies. A nested case-control study was carried out in all hospitals in İzmir. Controls were matched with cases on an individual basis according to the newborn's age and hospital in which they were born. There were 56 newborns with NTD out of 36,331 deliveries in İzmir hospitals in 2000. The incidence of NTD was 1.5 per 1000 births. Forty-four cases and 88 controls were analyzed for risk factors. According to chi-square analysis, maternal education, paternal education, maternal nutritional status, maternal drug usage, and presence of maternal chronic diseases and acute infections during pregnancy were found significantly different between case and control groups.

Key words: neural tube defects, case-control studies, pregnancy, risk factor.

Neural tube defects (NTDs) are congenital malformations resulting from complete or partial failure of the neural tube to close in the developing embryo. Anencephaly and spina bifida, comprising the vast majority of NTDs, are common congenital anomalies substantially contributing to morbidity and mortality, particularly in infancy and childhood. It has been estimated that one out of four affected fetuses will be stillborn, one of two will result in spontaneous abortion, and the remaining one will probably survive[1,2].

The majority of survivors require lifetime medical support, including shunting for hydrocephalus, and management of urologic and orthopedic deformities. Nutritional factors appear to be an important contributor to the etiology of many NTDs occurring in the population. Several other maternal factors have also been established as a risk for NTDs, including socioeconomic class, various environmental factors, genetic factors, and maternal illness or medication during pregnancy[3].

There is no ongoing surveillance system of congenital anomalies in Turkey. The incidence of NTDs in İzmir is currently unknown. A previously reported study refers to figures obtained from a single hospital following the Chernobyl disaster. The aim of this study was to calculate current incidence and prevalence figures of NTDs in İzmir, and to evaluate probable factors that may be attributed to causing NTD-affected pregnancies. Another objective of the study was to emphasize the importance of establishing a national surveillance for congenital malformations.

Material and Methods

The study was conducted between 1 January-31 December 2000. Formal permission for the study was obtained from the Ministry of Health and hospital management. We conducted a nested case-control analysis where all cases were compared to a group of controls derived randomly from the base population of the identified cohorts.

Hospitals included in the study were two university hospitals, three state hospitals, one municipality hospital, one social security hospital, and six private hospitals. All hospital deliveries were included. The study was conducted in two parts. First, we determined the incidence of NTDs (cases identified at birth) in a cohort of all the hospital deliveries in the year 2000. We registered 36,331 deliveries, all performed in the above-mentioned 13 hospitals

in İzmir. The Ministry of Health reported 41,774 registered deliveries in İzmir in 2000[8]. Thus, 93.4% of all births were included in this study.

Inclusion criteria were defined as women whose babies were affected by one or more of the following: anencephaly, encephalocele, spina bifida aperta, and spina bifida occulta. These NTDs occurred either alone or in combination with other birth defects in a live or stillborn baby following delivery in the listed hospitals in İzmir. Stillbirths referred to all fetal deaths of 24 weeks' or longer completed gestation. Myelomeningocele and encephalocele were obvious at birth. The signs of occult spinal dysraphism were noted.

The second part of the study was case-controlled. Children with the signs of occult spinal dysraphism were not included in the second part of study. Two age-matched healthy controls from live newborns with no anomalies were randomly selected for each case at the time of diagnosis (index date). Controls were matched with cases on an individual base according to newborn age and the delivering hospital. Fifty-six cases were detected in this cohort. Eight (14%) refused or missed participation in the second part of the study. Mothers of 10 cases did not complete a food-frequency questionnaire. One hundred and thirty-two women (44 cases, 88 controls) participated in the second part of the study and completed an interviewer-administered questionnaire.

The pre-trained interviewers (physicians and midwives) working in the hospitals administered the questionnaire on face-to-face basis to all cases and controls before they were discharged from the hospital. Education of the midwives, particularly on signs and symptoms of NTDs, was carried out in December 1999.

After obtaining the mothers' informed consent, the interviewers asked them to fill out the questionnaire which included questions on drug use, possible contact with toxic substances through work or the pursuit of hobbies, reproductive and family history, nutritional intake, and periconceptional use of oral contraceptives. There were also questions regarding maternal illness: diabetes, asthma, cancer or tumors, epilepsy or seizures, high blood pressure, thyroid condition, and infectious diseases; other questions concerned any medication taken for their illness during pregnancy. The same questionnaire was administered to two matched controls for each NTD case.

A short, qualitative 15-item food-frequency questionnaire was used. It was prepared by reviewing the literature and consulting the opinion of a dietitian[5-7]. The portion sizes were not recorded in the frequency history, so no attempt was made to convert consumption per g/day. This was a quick macroscopic view on the nutritional well being of the mother.

The participant was asked how often on average during the pregnancy she had consumed each food: cheese, bread, milk and dairy products, fruits and vegetables, egg, meat (beef, poultry and fish), and grain. Six responses were possible, ranging from "never or less than once per month" to "at least once per day". Each answer had a numerical value (0-5) and the final score had a maximum value of 50. If the resulting score was less than 41 (mean score), the mother was considered poorly nourished during the pregnancy.

Associations between NTD and the independent factors mentioned above were analyzed using the Mantel-Haenszel method. The Student's-t test (continuous variables) was used to compare means. Data were analyzed using SPSS 10.0 (SPSS Inc, Chicago, Illinois, USA). Statistical significance was accepted at the $p<0.05$ levels.

Results

There were 56 newborns with NTD out of 36,331 deliveries in İzmir hospitals in 2000. The incidence of NTDs was 1.5 per 1000 births. The incidence of NTD was 1.2 per 1000 births in the Social Security Hospital, 2.4 in two of the State Hospitals, 1.3 in two University Hospitals and 1.7 in one private hospital. There was no NTD case in the other seven hospitals.

Forty-eight of all newborns with NTD were evaluated. Their diagnoses were anencephaly (n: 4), encephalocele (n: 1), spina bifida aperta (n: 38), spina bifida aperta with encephalocele (n: 1), and spina bifida occulta (n: 4). Other congenital abnormalities combined with NTD were hydrocephalus (n: 13), and foot anormalies (n: 8).

The percentage of the preterm deliveries was 40.4 among NTD cases. The percentage of stillborns identified among NTD cases was 27.1.

Sociodemographic factors, maternal smoking habits, parental occupational history, potential exposure to drugs, pregnancy history and birth characteristics are depicted in Table I and II.

Table I. Parental Characteristics According to Case-Control Study Group

	Case (N: 44) (%)	Control (N: 88) (%)	X^2 (p-value)
Previous stillbirth	4.2	5.2	
Previous NTD	2.1	1.0	
Maternal occupation			
Housewife	91.3	90.7	
Any occupation	8.7	9.3	
Paternal occupation			
Unemployment	4.2	3.1	
Worker	45.8	26.8	
Civil servant	12.6	19.5	
Self-employment	37.4	50.6	
Maternal education*			20.89 (<0.000)
Illiterate	21.3	5.5	
Primary school	70.2	61.5	
High school	6.4	25.8	
University	2.1	7.2	
Paternal education*			9.70 (<0.021)
Illiterate	2.1	–	
Primary school	63.8	44.3	
High school	27.7	45.4	
University	6.4	10.3	
Consanguineous marriage	22.2	16.5	
Vitamin intake by pill during pregnancy	66.0	75.0	
Oral contraceptive before pregnancy	15.2	12.4	
Smoking during pregnancy	20.5	16.5	
Alcohol during pregnancy	4.5	1.0	
Acute infectious diseases*	18.2	2.1	12.20 (p: 0.0004)
Chronic diseases*	28.3	5.2	13.87 (p: 0.0001)
Maternal nutrition during pregnancy*			
Poor	60	10.3	35.07 (p: 0.00000)
Good	40	89.7	
Medication during pregnancy*	34.0	7.2	16.48 (p: 0.00004)
Delivery by			
Cesarian section	43.8	22.7	
Vaginal	54.2	75.3	
Forceps or vacuum extraction	2.0	2.0	

* Difference between case and control statistically significant.

Table II. Some Reproductive Parameters of Case and Control Groups

		Mean	SD	Significance
No. of abortions	Case	0.27	0.57	
	Control	0.39	0.67	
No. of pregnancies	Case	1.66	1.62	
	Control	1.14	1.20	
Maternal weight gain (kg)	Case	9.91	4.74	
	Control	10.06	4.90	
Gestational age (week)	Case	34.45	7.59	t: 6.163
	Control	39.31	1.25	p: 0.00
Maternal nutritional score	Case	37.52	7.56	t: 6.501
	Control	43.60	3.32	p: 0.000
Maternal age (year)	Case	27.16	5.43	
	Control	27.43	6.14	
Paternal age (year)	Case	30.91	5.90	
	Control	31.24	6.50	

Of cases mothers, 2.1% had previous babies with NTD compared to 1% of control mothers; this difference was not statistically significant. The percentage of consanguineous parents was 22.2% among cases, which was not significantly different from the control group. There was no statistical difference between case and control groups. Vitamin supplements were taken by 66% of the cases during their pregnancies. The number of parents of babies with NTDs with

a lower educational status was significantly higher than that of control group mothers. There was no association between NTDs and parental consanguinity, parental occupation, maternal alcohol consumption, and smoking.

Chronic diseases (diabetes, cardiovascular disease, epilepsy, etc.) and acute infections (urinary, gastrointestinal, respiratory, etc.) were more prevalent among case mothers. The presence of maternal chronic disease during the pregnancy period was significantly more frequent within mothers of babies with NTDs (OR: 2.52, 95% CI: 1.20-5.31). The odds ratio (OR) of Mantel and Haenszel resulting from associated acute infectious diseases and NTD was 3.65 (95% CI: 1.05-12.68).

Among mothers of control infants, and of infants with NTD, reported medication usage during pregnancy period was 7.2% and 34.0%, respectively. Drug intake during pregnancy was identified as a risk for NTD development (OR: 6.65, 95% CI: 2.26-20.2).

Maternal nutritional intake was one of the risk factors for NTDs. It was found that cases mothers had inadequate weight gain during pregnancy. The mean gestational age was significantly lower among cases than controls (Table II). The mothers who were poorly nourished during pregnancy were more prevalent among the case group (chi-square: 35.07, P: 0.000). The OR for maternal nutrition was 4.89 (CI, 2.84 to 8.42). Control group mothers consumed more dairy products, fruits and vegetables, meat and bread than NTD mothers did. Almost 2% of mothers of cases ate meat daily. The most frequently consumed foods on a daily basis were bread, cheese, vegetables and fruits (Table III).

Table III. Nutritional Daily Intake by Case and Control Study Groups

Food items	Case N: 44 (%)	Control N: 88 (%)
Meat, poultry, fish	2.2	9.3
Cheese	69.6	96.9
Milk	28.3	82.5
Yoghurt	58.7	87.6
Egg	30.4	71.1
Vegetables	63.0	94.8
Fruits	63.0	93.8
Bread	60.9	96.9
Grain	34.8	33.0
Dry beans	13.0	11.3

Discussion

Neural tube defects are considered to have one of the highest incidence rates of all the congenital malformations. NTD rates vary from one population to another, and have also been found to vary by geography, time, and selected maternal demographic characteristics. Occasionally rates as high as 1% have been reported[9]. Infant deaths attributable to NTD as a percentage of total infant deaths has fluctuated around 3.5%[10].

Neural tube defects can be detected antenatally through maternal serum alpha-fetoprotein screening or prenatal ultrasound tests. This screening and periconceptional folic acid supplementation has substantially decreased the incidence of NTDs in some countries. These facts must be taken into consideration when comparing incidences among countries with different practice patterns in prenatal care[11].

There has been no multi-centric hospital-based study for congenital malformations in İzmir. All maternity hospitals in İzmir were involved in this study. The incidence of NTDs was 1.5 per 1,000 newborns in İzmir in our 2000 cohort. This incidence had been reported as 1.9 per 1,000 among those conceived prior to May 1986 in a Social Security hospital in İzmir. However, among conceptions occurring in May, June and July 1986, the NTD rate increased to a level of 8.9 per 1,000, subsequently gradually declining to previous levels within nine months. In all there were 19,115 births between June 1986 and July 1988[4]. We found that incidence of NTD was 1.2 per 1,000 births in this hospital. A small decrease was observed in a 16-year period in our region.

The incidence of NTDs was 2.12 per 1,000 births in a hospital in Trabzon during 1981-1986[12]. The incidence of NTDs was 0.27% in Gazi University Medical School during 1988-1995 in Ankara[13]. Tunçbilek[14] reported that the prevalence rate of NTDs was 30.1 per 10,000 births at the university hospitals throughout Turkey between July 1993-June 1994. Of the 5,240 newborns, 24 had a neural tube defect, giving a birth prevalence of 4.5 per 1,000 total births during 1985-1990 in Elazığ, eastern Turkey[15].

Age, race, education, economic status, access to health care, women's dietary practices, nutritional status, exercise habits, and other lifestyle patterns both before and during pregnancy had a significant impact on maternal

and infant health[16,17]. Maternal illiteracy, advanced age and being settled in northern or eastern regions of Turkey were risk factors for having a baby with a NTD according to Tunçbilek et al.[14] Farley et al.[18] reported that low maternal education was an important predictor in having a child with NTD. Similarly, we found that educational levels were strongly related with occurrence of NTD in an İzmir cohort.

It was reported that both lower socio-economic status (SES) and residing in a lower SES neighborhood increased the risk of an NTD affected pregnancy, with risks increasing through a gradient of SES indicators[19]. Geographical distribution of NTDs in Turkey confirms a relationship between the SES and environmental factors for the development of NTD[14]. İzmir has a population of 3,370,665 with different socioeconomic classes. There is a high migration especially from eastern Turkey. Most of the deliveries were performed at Social Security and State Maternity Hospitals in İzmir. Middle or lower socioeconomic level individuals attend these hospitals.

The expected weight gain of a pregnant woman with normal weight is 10-12 kg. While mean weight gain in mothers of the control group was 10.0619±4.9028 and was 9.9143±4.7426 in case mothers. Gestational weight gain has been reported to vary by SES in the US; low weight gains appear to be more common in women with lower educational status[19].

There was a significant difference between the case and control groups according to gestational age and delivery types. In Turkey, most physicians suggest preterm induced delivery for mothers who have a child with anencephaly. In addition they prefer cesarean section for delivering a child with NTD.

There was an association between NTD and maternal nutritional deprivation in our study. This relationship may be explained by folate- or other micronutrient-deficient diet. All of the micronutrients are present in meat, fish, milk, poultry, fruits and vegetables. A Turkish traditional meal today might include any of these foods. In addition, these foods are widely available. Izmir is one of the Mediterranean Sea cities with a high variety of seafood. Nutritive restrictions are usually the result of lower socioeconomic status or parental education. People of lower SES tend to consume diets that contain more bread and sugar and less fruit, vegetables or meat. In Turkey, the female adult literacy rate was 75.9% and GDP per capita was US$ 6380 in 1999. But economic inequality existed not only in terms of regions, income, knowledge and gender, but also across households and residence[20]. The impact of the economic crisis on the lower class and unemployment is serious in Turkey. Kramer et al.[21] reported that the rates of adverse pregnancies generally rise with increasing socio-economic disadvantage, and suggested that it might not be possible to eliminate the higher risks of adverse pregnancies among the poor unless the poverty itself is eliminated. Our findings are supported by previous evidence that poor maternal nutrition and low dietary folate in particular increase the chance of having a child with a NTD and emphasize the need for supplementary folate in the diet of women of childbearing age in areas where the frequency of NTDs is high[22-24]. Shaw et al.[25] observed reduced risks with increased intakes of grains and dairy products. It was claimed that the effects of the war famine of 1945-46 in the Netherlands caused the infants to be exposed to famine during early gestation. There was a significant increase in the incidence of meningomyelocele. Food shortages in Second World War Norway and post-war Germany showed similar results[26].

Maternal zinc deficiency was thought to be one of the factors responsible for NTD in Turkey[27]. The percentage of acute infectious diseases was significantly higher among case mothers in our study. Some studies have implicated maternal hyperthermia or fever-producing illness as a risk factor for NTDs[28]. Consanguineous marriage has a significant influence on child mortality and morbidity[29], and they are common in Turkey. This rate is 25.1% according to the Turkish Demographic and Health Survey in 1998[30]. There was no association between NTD and consanguineous marriage in our study.

Advanced maternal age has been recognized as a higher risk for a number of adverse outcomes, including fetal loss, premature birth, low birth weight, certain types of birth defects and infant mortality[29,31]. Our case and control study group included younger mothers.

Twenty-eight percent of the mothers of cases and 5% of control mothers had chronic diseases, resulting in an odds ratio of 2.52

(95% CI: 1.20-5.31) in the İzmir cohort. Epidemiologic studies specifically investigating NTD risks associated with maternal illness or medication are relatively few. Increased NTD risks have been associated with maternal conditions and treatment, such as insulin-dependent diabetes and epilepsy, the risk being significantly higher for epileptic women[28,32].

The percentages for smoking and alcohol consumption were found higher among mothers of cases. But there was no statistical difference between cases and controls. Yet very different rates of substance use are reported for different population groups in different studies. Overall, values for alcohol and illicit drug use for pregnant women are substantially lower than those for non-pregmant women[16].

Loncorek et al.[11] reported that cartography of NTDs, identification of prevalence in certain regions and populations, and likewise the detection of secular trends will be of substantial importance in searching for causative and protective factors.

The benefit of folic acid in reducing the prevalence of NTDs is well established. But an expanded program or campaign for prevention of NTDs has not been conducted in Turkey, instead there is a Ministry of Health folic acid project. There is no information on the proportions of women taking periconceptional folic acid supplements, or of health professionals advising women planning a pregnancy about folate. Surveillance data is useful for developing prevention or intervention programs. Systematic monitoring of birth defects in Turkey is vital, and our multicentric cohort study could be a preliminary report for future programs.

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