NEURAL TUBE DEFECTS AND RECURRENCE RISKS IN ONE REGION POPULATION OF TURKEY*

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SUMMARY : Our aim was to evaluate the neural tube defect profile in a certain population of Turkey. For this purpose we investigated the sex ratio, maternal and paternal ages, birth places of propozitus and parents, consanguinity, other malformations associated with neural tube defects (NTD) and recurrence risks in the sibs of the 269 patients with neural tube defects referred to our Department. It seems that recurrence risks are higher than other populations.

***Key Words** : Neural Tube Defects, Recurrence Risk.*

INTRODUCTION

Neural tube defects are a variety of malformations resulting from incomplete closure of the neural tube in the early development of the fetus and thought to have a common multifactorial etiology including both genetic predisposition and environmental factors (3). In the majority of the cases spina bifida (encephalocele, meningocele, meningomyelocele) and anencephaly, sometimes occuring in combination are found. A single specific genetic marker has not been identified in view of the heterogenous nature of this disorder and the multifactorial inheritance is attributed to the additive effects of several minor gene abnormalities.

We here present our experience with the condition in order to estimate recurrence risks for a better counselling.

MATERALS AND METHODS

Data presented here were gathered from the files pertaining to families living in the middle Anatolia and referred to our Genetics Service because of a neural tube defect between the years 1979-1989. Stories were taken in the presence of both parents and all available records were included into the files. 269 (121 males and 148 females) cases with NTD were collected into 3 groups as shown in table 1. In 48 of these delineation of the malformation could not be possible; however, they were not excluded because we were dealing with the overall recurrence risks.

Results were tested by chi-square test.

RESULTS

1- SEX RATIO : Out of 269 NTD cases 121 (44.88 percent) were males and 148 (55.02 percent) were females, giving an excess of females, the sex ratio M/F : 121 / 148 being 0.81 (Table 1).

2- MATERNAL AGE : Age of mothers varied from 17 to 35 with a mean of 24.2±4.02 years. The distribution is compatible with the conclusion that maternal age would not be a factor in the genesis of

	MALE		FEMALE		TOTALS	
NTD	n	%	n	%	n	%
Anencephaly	25	9.29	43	15.98	68	25.28
Spina bifida	67	24.91	86	31.97	153	56.88
Unspecified	29	10.78	19	7.07	48	17.84
TOTALS	121	44.98	148	55.02	269	100

Table 1 : Sex distribution of cases with neural tube defects.

the malformation.

3- PATERNAL AGE : The same holds true for the paternal age. The range is from 19 to 42 with a mean of 27.73=4.46 years. No contribution of paternity to the defect could be shown.

4- BIRTH PLACE : Birth places of both parents and the living place of the family were evaluated. Naturally, any fetus with NTD should be considered within the later category. As it can be seen from Table 2, parents from villages and small towns are in excess having an offspring with NTD. It is also apparent that birth places do not provide evidence that parents were from a certain area. On the other hand, fewer parents live in th : villages than those in bigger cities (Table 3) due to continious migration within the country.

5- FETUS OR INFANT WITH NTD : The fate of a zygote after the development of a neural tube defect is extremely variable (Table 4). While 0.38 percent of such fetuses abort spontaneously; 3.35 percent are induced to born. Some 35.68 percent are stillborn and the remaining 55.76 percent die early in life. As it can be seen from the Table, at least % 95 of the infants die within first years of life, so that the condition apparently is not compatible with a normal life. Only some 5 percent survive.

6- NTD AND OTHER CONDITIONS AMONG SIBLINGS : Total number of conceptions before or after the propositus under consideration is 406 (Table 5). Because of the retrospective character of this work entities other than NTD among the siblings of the propositus have not been taken into account. There were 71 such cases 34 of

BIRTH PLACE OF THE FATHER								
Village		Town		City		Unknown		Total
n	%	n	%	n	%	n	%	n
105	39.03	96	35.67	56	20.83	12	4.47	269
BIRTH PLACE OF THE MOTHER								
102	37.91	92	34.2	67	24.91	8	2.98	269
207		188		123		20		538

Table 2 : Birth places of both parents with a fetus or infant with NTD.

LIVING PLACE OF THE FAMILY									
Village		Town		City		Unknown		Total	
n	%	n	%	n	%	n	%	n	%
30	11.15	43	15.98	196	72.87	-	-	269	

Table 3 : Living places of parents with a fetus or infant with NTD.

Spontaneously aborted		Induction		Stillborn		Dead after liveborn		Surviving		
n	%	n	%	n	%	n	%	n	%	T
1	9	9	3.35	96	35.68	150	55.76	13	4.83	269

Table 4 : The fate of a zygote developing NTD.

ENTITY	n	%
Spontaneous abortion	83	20.44
Induced abortion	18	4.43
Criminal abortion	17	4.19
Stillbirth	35	8.62
Death (from other causes)	75	18.47
Alive (affected with an other malformation/disease)	11	2.71
Healthy and normal	96	23.65
NTD	71	17.49
TOTAL	406	100

Table 5 : Fate of other conceptions before or after the birth of the propositus.

which were males (43.04 percent), 38 (48.10 percent) were females and the remaining 7 (8.86 percent) had unspesified sex. It has previously been reported (12, 18) that NTD is more prevalent among females. The type of the defect in the sibling is shown in Table 6. Some of these were accompanied by defects of other organs such as limb malformations, polydactyly, etc.

ENTITY	n	%
Anencephaly	18	25.35
Spina bifida	13	18.3
Meningocele	5	7.04
Meningomyelocele	16	22.54
Unspecified	19	26.76
TOTAL	71	100

Table 6 : NTD among siblings of the proband.

It is also interesting that NTD was more frequent in first pregnancy ($p<0.01$).

7- TWINNING : There were two sets of twins (0.74 percent), one being dizygotic and the other monozygotic. In the first pair one member was normal and the second anencephalic whereas one member was anencephalic and the other was stillborn without an apparent abnormality in the other member of second twins.

8- CYTOGENETICS : Since the work was retrospective, only 3 cases were available for chromosomal study. In two of which chromosome complement was normal, but in the third tetraradial configurations were observed which remain unexplained. On the other hand, no consistent abnormality was discovered among the parents.

9- PARENTAL CONSANGUINITY : Parental consanguinity was found in 104 cases with a rate of 38.66 percent. This was very close to the rate found in the Genetics Services Department, concerning the proband and his (her) spouse. First - cousin marriages were the most frequent (69.23 percent) and this was the same for other studies too (29). Recurrence of NTD in subsequent pregnancy noted in 28 families with a consanguinity rate of 26.9 percent and the observation of occurrence of the affliction in 3 consecutive conceptions in 4 families suggest that autosomal recessive genes play a role in the etiopathogenesis of NTD.

10- OTHER MALFORMATIONS : Neural tube defect has been described associated with other organ malformations. Because most of these affected cases were not accessible for study, no comments have so far been made but they only were listed in Table 7.

ENTITY	NO OF PROBANDS HAVING OTHER MALFORMATION
Craniorachischisis & horse - shoe kidney	1
Polydactyly	4
Clubfoot	12
Bilateral surrenal hyperplasia	1
Growth retardation	1
Skelatel anomalies	3
Bilateral inguinal hernia	2
Hearth defect	1
Adrenal hemorrhage	1
Eye malformation	1
Genital anomaly	1

Table 7 : Other malformations associated with NTD.

11- RECURRENCE RISK : While determining the risk, spontaneous and unwanted abortions were excluded from consideration. The risk of recurrence of a neural tube defect in the subsequent pregnancy was estimated to be 23.2 percent as a whole that is somewhat higher than those reported from other populations. On the other hand while the risk was 32.8 percent to consanguineous parents, it decreased to 16.57 percent in non-consanguineous ones. In 7 families (2.28 percent) there were 2 more effected sibs after the index patient.

DISCUSSION

Incidence of neural tube defects varies from 0.47 to 8.87/1000 in different countries (3.5-10). Viral, chemical, nutritional factors, seasonal variations on the date of conception, geographic and ethnic-group differences, minor or major gene defects (9), and consanguinity (13) have all been postulated as influencing factors in development of a defect of this type. There is a female preponderance (12, 18).

Carter et al. reported the sex ratio 0.79 (M/F) and 0.41 for spina bifida and anencephaly, respectively, in a total of 631 births (3). Bargainer et al. found a higher female ratio of 3:1 for anencephaly and 1.3:1 for spina bifida (2). Similarly, in this study we observed an excess of females with a sex ratio of 0.81, 121 males against 148 females being affected. These lend support to the suggestion (21) that female fetuses likely have a higher treshold. Numerous investigators have attemped to associate a variety of environmental factors or agents with the occurrence of NTD, as in the case of chromosomal disorders, one of them being maternal age (2). Carter and Evans reported more mothers than expected among index patients either under the age of 20 or over 35 (33). Yen (33) has shown a relatively slight effect of maternal age and parity, while Hall et al. found no significant effect of proband's mother's and father's ages at conception (12). In this study we could not observe any effect of maternal and paternal ages on the genesis of the malformation (Fig 1, 2).

It has been proposed that socioeconomic factors play an important role in the formation of neural tube defects (21, 22). The importance of social class was shown clearly by Edwards in 1958 (3) and later confirmed by other investigators (3, 21, 22). In the present study the number of affected children whose parents were born in villages and towns were comparably higher than those with parents born in bigger cites. This would appear consistent with the effect of socioeconomic factors on incidence of NTD (3, 16). Although diet appears as an immediate variable it is nesessary to define clearly the food intake and beverages in families sometime before conception and during early gestation. Works in our country evidently reveal that dietary Zn (zinc) is of outmost importance (8, 23). Anomalies associated with NTD include cleft lip and palate, tracheo-oesophageal fistula (10), congenital heart defects, urogenital abnormalities and hip dislocation (12, 13, 17, 19, 24, 29, 31, 33). In 10.4 percent of our patients NTD was associated with other anomalies like club foot (n=12) being the most frequently observed malformation (Table 6). Hall et al, found the frequencey of congenital anomalies secondary to NTD in their series as 14.5 percent and suggested that it may indicate multiple effects of a common insult to embryogenesis or to common developmental pathways, or both (12).

Fuhrmann et al. have reported in 1971 two consanguinous couples with multiple occurence of NTD in the offspring (31). In a total of 479 cases, Stephan et al have found % 1 of their patients had a first-degree relative with NTD and a further % 1 a first-degree relative with cleft lip and/or palate (31). On the other hand Carter et al (3) have reported no increased proportion of affected sibs with parental consanguinity. The figure is quite different for our country where the rate of consanguinous marriages is rather high (% 12) especially in rural areas (29). In an investigation on Turkish children Sainio et al. have revealed the occurence of NTD for the first-cousin marriages as 9.8 percent while it decreased to 6 % in non-consanguineous control group (28). we also found a high consanguinity rate (38.6 %) in our group, among these first-cousin marriages (69.2 %) being most frequent. Sainio et al. (28) reported 14.3 percent recurrence risk of NTD for blood-related couples but 4.5 percent for unrelated ones (28). We found 32.8 % recurrence risk for blood related parents and 16.5 % for non-consanguineous families; although significant, the reason of this difference is not clear. This might be due to autosomal recessive syndromes in which NTD occurs. The risk of recurrence has been estimated between 0-10 percent for different populations and by various authors (2, 17, 25, 29, 32). A significantly-high recurrence risk for subsequent pregnancies observed in this study may be due to high consanguinity rate, nutritional habits (especially low Zn intake) ethnic and geographic differences in or population compared to those of other reports (20, 30).

In conclusion our high recurrence rate of NTD in a sample of Turkish population from Middle Anatolia may be explained by high consanguinity rate (possible effect of major as well as minor genes) and the widely observed social-class factor in the incidence of NTD also suggest the possibility of a nutritional contribution.

To day prenatal diagnosis is widely used to diagnose and terminate the fetus with NTD. In the period between 1979-1989 prenatal diagnosis of NTD with ultrasonography and high levels of α-fetoprotein was available only in 9 fetuses (% 3.35) of our study group and were inductively aborted.

The incidence of the malformation is also reduced by prenatal diagnosis and periconceptional vitamin (14) and zinc (8) supplementation.

It appears clear that more data are needed to estimate the recurrence risks of neural tube defects in Turkish population.

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