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Incidence of neural tube defects in Afyonkarahisar, Western Turkey

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ABSTRACT. The incidence of neural tube defects is higher in Turkey compared to that of developed countries. To prevent congenital malformations, understanding of the current status is necessary, which should be followed by public-based activities. We examined the incidence rate of neural tube defects (NTDs) in Afyonkarahisar. According to the records of the Department of Pediatrics, Zubeyde Hanım Hospital for Children's and Women's Health in Afyonkarahisar, the total number of births was 8631 during 2003 and 2004. Sixty-three babies with anomalies were identified in the early postnatal period. The incidence of neural tube defect based on records of hospitals in the city center was calculated as 3.58/1000, among which 9 (1.04%) of the malformed babies had spina bifida, 2 (0.23%) had encephalocele, 12 (1.39%) had anencephaly, and 8 (0.92%) had meningocele/meningomyelocele. In 32 of the 63 cases, there were also other malformations (cleft lip or clubfoot, hydrocephalus, foot abnormalities, etc.). We calculated the total incidence of NTDs, including live births, stillbirths and therapeutic abortions. Stillbirths referred to all fetal deaths after 24 weeks or longer gestation. In each case, the type of anomaly was determined. Thirty-one babies with an NTD were recorded among 8631 gestations (all live births, stillbirths and therapeutic abortions). The incidence of NTDs was found to be

35.9 per 10,000 live births in Afyonkarahisar. The incidence of spina bifida/anencephaly was 0.748 per 1000 newborns. Maternal illiteracy, maternal advanced age and residence in northern or eastern regions of Turkey were found to be risk factors for having a baby with an NTD. The incidence of NTDs is higher than in other European countries.

Key words: Neural tube defects; Spina bifida; Anencephaly; Mutation; Birth defects

INTRODUCTION

Neural tube defects (NTDs) are one of the most common birth defects (Melvin et al., 2000). NTD results in congenital malformations of the nervous system (Moore, 1982) and may lead to spontaneous abortion, stillbirth, death in early infancy, or lifetime disability (Gucciardi et al., 2002). An NTD is an opening in the spinal cord or brain that occurs very early in human development. The early spinal cord of the embryo begins as a flat region, which rolls into a tube (the neural tube) 28 days after the baby is conceived, and when the neural tube does not close completely, an NTD develops. NTDs develop before most women know they are even pregnant (Melvin et al., 2000).

There are two types of NTDs. The most common types of NTDs are called open NTDs. Open NTDs occur when the brain and/or spinal cord are exposed at birth through a defect in the skull or vertebrae. Examples of open NTDs are spina bifida (myelomeningocele), anencephaly, and encephalocele. The rarer types of NTDs are called closed NTDs. Closed NTDs occur when the spinal defect is covered by skin. Common examples of closed NTDs are lipomyelomeningocele, lipomeningocele, and tethered cord (Melvin et al., 2000).

The neural plate appears during the third week of gestation and gives rise to the neural folds that fuse in the midline to form the neural tube. Recent animal and human data suggest that neural tube closure occurs in multiple regions, which then fuse (Van Allen et al., 1993; Seller, 1995). Defects result either from the failure of closure of one site or failure of two sites to meet. Neural tube closure is normally complete by the end of the fourth week after conception (6 weeks after the last period), a time when many women do not yet realize they are pregnant. NTDs are common congenital malformations that appear mainly as anencephaly, encephalocele and spina bifida (ACOG, 2003).

Spina bifida and anencephaly are generally considered as one entity because both defects can run in the same families (Fuhrmann, 1971), and that is probably the reason why so many studies group these two defects together. It is very likely that spina bifida and anencephaly share some mechanisms but they should always be considered independent entities (Vieira, 2004). NTDs are considered to be etiologically multifactorial, which require both genetic suspectibility and environmental risk factors. Mutations and polymorphism in folate pathway genes such as methylenetetrahydrofolate reductase, methionine synthase and methionine synthase reductase have been broadly investigated, with some studies showing an association with NTD risk (van der Put et al., 2001; Zhu et al., 2003, 2004).

Several studies have reported an independent effect of maternal age and birth order on NTDs (Fedrick, 1970; Naggan, 1971; Hay and Barbano, 1972; Granroth et al., 1978; İmaizumi, 1979; Feldman et al., 1982). Older mothers are known to be at a higher risk for trisomy 13, 18

and 21. Spina bifida is not frequently reported for Down syndrome, but is present in less than 50% of trisomy 13 cases and in less than 10% of trisomy 18 cases (Jones, 1997). One substantive confounder of maternal age, and therefore birth order, is paternal age. Although later paternal age is associated with increasing mutation rates, many studies have considered paternal age and only one of which found a general pattern of increasing risk for NTDs associated with advancing paternal age. The majority of studies have failed to show a relationship between paternal age and risk for NTDs (Czeizel and Révész, 1970; Strassburg et al., 1983; Frecker and Fraser, 1987; Simpson et al., 1991; Chatkupt et al., 1994; Shaw et al., 1994).

Known environmental factors include folic acid, maternal insulin-dependent diabetes, and maternal use of certain anticonvulsant (antiseizure) medications. Several studies demontrated that the study population is unaware of the importance of folic acid for preventing NTDs. Folic acid is a water soluble "B" heat-labile vitamin that was first isolated from spinach leaves. Folic acid acts as a coenzyme for one-carbon transfer reaction, and is essential for growth, cell differentiation, methylation, gene regulation, repair, and host defense (Jaber et al., 2004).

The aim of the present study was to determine the incidence rate of NTDs in Afyonkarahisar. All live births, stillbirths and fetuses at the Department of Pediatrics, Zubeyde Hanım Hospital for Children's and Women's Health in Afyonkarahisar from July 2003 to December 2004 were evaluated with respect to NTDs. The main purpose of this study was to determine the incidence of NTD in the Afyonkarahisar region. Data were obtained from the Department of Pediatrics, Zubeyde Hanım Hospital for Children's and Women's Health, Afyonkarahisar, Turkey. Although there may be many reasons for NTDs, we were unable to determine the etiological factors from medical records of the hospital.

MATERIAL AND METHODS

This study was conducted in the Department of Pediatrics, Zubeyde Hanım Hospital for Children's and Women's Health, in Afyonkarahisar, Western Turkey. Data collected on each case included date of birth by month and year. This study included, infants or fetuses who had anencephaly, spina bifida, or encephalocele and other NTDs identified at birth or prenatally, between July 2003 and December 2004. Cases included diagnoses made among live births, stillbirths and abortions, whether induced or spontaneous. We evaluated the data for total NTD incidence rate.

RESULTS

There were 8631 live borns during the study period, 31 of whom had NTDs, giving a birth incidence of 3.59 per 1000 total pregnancies in Afyonkarahisar (Figure 1). This rate is 4.5 for Eastern Turkey (Güvenc et al., 1993). While the incidence rate of NTDs was 30.1 per 10,000 at birth in Turkey (Tuncbilek et al., 1999), we found that it was 35.9 per 10,000 at birth in Afyonkarahisar. Anencephaly was the most common type of NTDs at 13.9% (12 in 8631 live births), following the spina bifida cases 10.4% (9 in 8631 livebirths), in our population. We found the rate of spina bifida/anencephaly to be 0.748 per 10,000 at birth in Afyonkarahisar. This rate was reported to be 1.20 for Turkey (Tuncbilek et al., 1999). Other NTD percentages with respect to frequency were as follows: meningomyelocele/myelocele 9.2% (8 in 8631 live births) and encephalocele 2.3% (2 in 8631 live births) (Table 1).

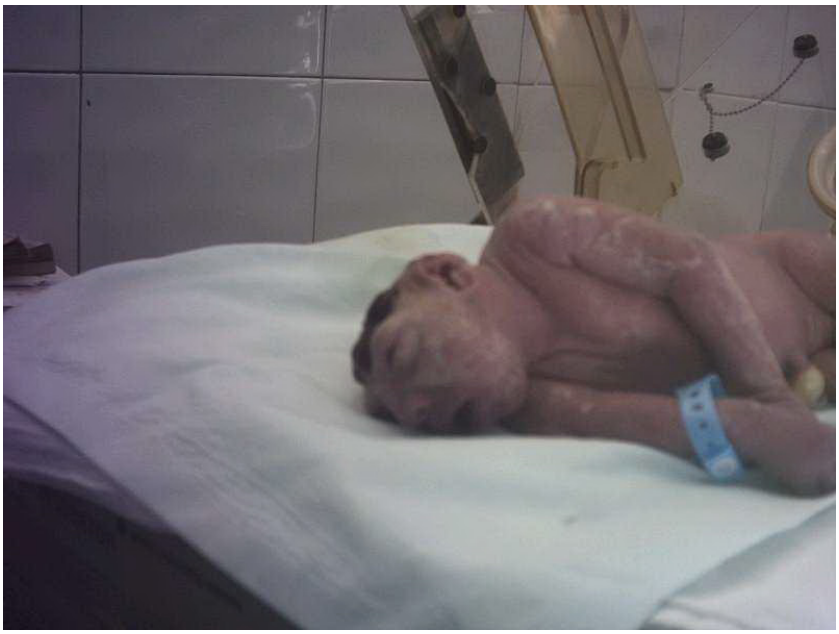

Figure 1. Anencephaly is readily apparent at birth because of the absence of the skull and scalp and exposure of the underlying brain. The condition is also called acrania (absence of the skull) and acephaly (absence of the head). In its most severe form, the entire skull and scalp are missing. In some cases, termed "meroacrania" or "meroanencephaly", a portion of the skull may be present. In most instances, anencephaly occurs as an isolated birth defect with the other organs and tissues of the body forming correctly. Patient with anencephaly was seen in the Department of Pediatrics, Zubeyde Hanım Hospital for Children's and Women's Health, in Afyonkarahisar, Western Turkey.

Table 1. Incidence of neural tube defects (NTD) in Afyonkarahisar, Western Turkey, 2003-2004.

NTD	NTDs/8631 live births	NTD/1000
Spina bifida	9	1.04
Anencephaly	12	1.39
Encephalocele	2	0.23
Meningocele/meningomyelocele	8	0.92
Total	31	3.58

DISCUSSION

The etiology of spina bifida/anencephaly and other neural tube defects is probably multifactorial and results from the combined actions of genetic and environmental factors.

Akar et al. (1988) reported that a radiological survey of 1204 members of the population of Bursa revealed a high incidence of spina bifida occulta (16.3%). Hospital deliveries in the area also showed a high incidence of anencephalus and spina bifida aperta (5.8 per 1000 total pregnancies) in the years 1983 to 1986. We found it was 0.74 per 1000 at birth in Afyonkarahisar. The value we found is lower than that reported by Akar et al. This is due to the fact that NTDs are near the region that was affected by the Chernobyl disaster (Akar et al., 1989).

Mocan et al. (1992) reported that after the Chernobyl disaster, attention was focused on the effect of radioactivity on the conceptus, especially during early embryogenesis. In several recent studies from Turkey, marked increases in incidence of anencephaly were shown (Akar et al., 1988; Çağlayan et al., 1989; Mocan et al., 1990). However, such increases have not been identified from the EUROCAT malformation registry in other countries in Europe.

Mocan et al. (1992) studied the population of Ankara with the surrounding towns and villages, which was 3,235,637 in 1990. The incidence of NTDs prior to 1987 was 3.83 per 1000 births based on 125,839 deliveries compared with 2.53 per 1000 among 91,864 deliveries after January 1987; the incidence of anencephaly prior to 1987 was 2.59 per 1000 births and 1.25 thereafter.

Various authors have also reported a marked increase in anencephaly and other NTDs among conceptions occurring after the Chernobyl disaster in the Bursa (Akar et al., 1988), Agean (Çağlayan et al., 1989) and Eastern Black Sea (Mocan et al., 1990) regions of Turkey (Mocan et al., 1992).

Güvenç et al. (1993) reported that of 5240 newborns, 24 had a neural tube defect, giving a birth incidence of 4.5 per 1000 total births. Of these, 20 were anencephalic (3.8 per 1000). In all, of the 2355 conceptions estimated to have occurred prior to the Chernobyl disaster in May 1986, the birth prevalences of total NTD and anencephaly were the same (1.7 per 1000). This contrasts with the years following Chernobyl, when the birth prevalence of total NTD was 6.9 per 1000 (5.5 per 1000 for anencephaly). However, investigators have reported a birth incidence of 1.5 to 2.6 per 1000 births for Turkey (Say et al., 1973; Ilter et al., 1978; Buckley and Erten, 1979; Güvenc et al., 1989). Çağlayan et al. (1989) reported that the incidence then declined over the following 6-12 months and finally achieved the pre-Chernobyl level.

Himmetoglu et al. (1996) published that of the overall congenital anomaly incidence was 1.11% and the NTD incidence was 0.27% in their study population. Anencephaly was the second most common NTD with a proportion of 40%, following the spina bifida cases. There was a significant difference between female and male newborns with encephalocele.

Tunçbilek et al. (1999) observed that of a total of 21.907 live births and stillbirths examined, 66 cases with neural tube defects were recorded. The incidence rate of NTDs was 30.1 per 10,000 births. The 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%) cases with encephalocele. The ratio of spina bifida/anencephaly is 1.20 in Turkey, as it is in countries where the prevalence rate of NTDs is very high (Tunçbilek et al., 1999).

When compared with the EUROCAT registries (1997), Turkey has a very high incidence rate of NTDs. Within Europe, contrast in the epidemiology of NTDs is observed. The incidence was much higher in the British Isles than in continental Europe in the early 1980s (EUROCAT, 1987, 1997). Periconceptional use of folic acid by women of childbearing age lowered the incidence of NTDs significantly in England and Ireland. The trend in the incidence rate of NTDs confirms the impact of environmental factors, especially folic acid, on the etiology of neural tube defects. In Turkey, the incidence of NTDs is found to be very high when compared even with rates in the British Isles in the 1980s. The spina bifida/anencephaly percentage is low due to an increase of anencephaly cases when the incidence rate of total NTDs is high in the geographical region (Rankin et al., 2000). An inverse relationship between the male preponderance and the incidence of NTDs has also been suggested in different ethnic groups. According to 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. The average male

preponderance is 44% for all NTD cases, 33.3% for anencephaly cases and 55% for spina bifida cases. The agreement of our results with those of the EUROCAT study, particularly with the centers where NTD prevalence is high, confirms that accuracy of this study is more likely to have a lowering impact on the incidence rate of NTDs. The geographical distributon of NTDs in Turkey confirms a relationship between socioeconomic status and environmental factors for development of the NTD.

Rankin et al. (2000) reported on a population-based sample consisting of 984 NTDs: there were 403 (43.1%) with anencephaly, 472 (50.5%) with spina bifida and 59 (6.3%) with encephalocele. The total incidence at birth was 17.9 per 10,000 births. Maternal age-specific incidence rates decreased with increasing age.

Persad et al. (2002) published that in the period after supplementation initiatives were begun but before fortification was implemented, the incidence of open NTDs did not change significantly: the mean annual rate was 2.55 per 1000 births during 1991-1994 and 2.61 per 1000 births during 1995-1997. After the fortification was implemented the incidence of open NTDs decreased by more than 50%; the mean annual rate was 2.58 per 1000 births during 1991-1997 and 1.71 per 1000 births during 1998-2000.

Gucciardi et al. (2002) reported that the total NTD incidence rate increased from 11.7 per 10,000 pregnancies in 1986 to 16.2 per 10,000 in 1995, and it subsequently decreased to 8.6 per 10,000 by 1999. The NTD birth rate (live births and stillbirths) decreased from 10.6 per 10,000 births in 1986 to 5.3 per 10,000 in 1999. The rate of therapeutic abortions with an NTD or hydrocephalus rose from 17.5 per 10,000 abortions in 1986 to 50.7 per 10,000 in 1995 and fell to 28.7 per 10,000 abortions in 1999.

Various authors have reported an incidence of 1.8 to 2.6 per 1000 births in the Western regions of Turkey and two have noticed a marked increase in anencephaly and other neural tube defects among conceptions occurring after the Chernobyl disaster (Ilter et al., 1978). They claimed that this might be a coincidence but could also be due to the nuclear wave from Chernobyl affecting the conceptus after May 1986. The EUROCAT monitoring system (1988) showed no increase in rates of anencephalus after Chernobyl, but comparative data from other areas are urgently needed. There have, however, been no data from (eastern) Turkey. The current study was therefore undertaken.

When we compared our results with those of other studies, the incidence rate of NTDs is harmonious. The results presented here suggest that there may be a causative relationship with the B12 deficiency, radiation, methylenetetrahydrofolate reductase, maternal and paternal age, genetics and environmental factors.

In conclusion, congenital anomalies including structural malformations, chromosomal abnormalities and metabolic disorders are becoming the most important cause of perinatal mortality (about a quarter of all perinatal deaths) in the countries of Europe and, after prematurity, the second cause of infant morbidity. Surviving children with physical, mental and social handicaps are a significant burden on health and social services. Primary or true prevention is at present limited, e.g., folic acid can at best prevent only a small proportion of congenital anomalies. Tertiary prevention (corrective surgery or medical treatment of anomalies) is successful and curative for some malformations but also leads to increased survival of children with handicapping conditions with associated longterm morbidity. This has implications both for the affected child and its family in terms of suffering and also for society in terms of resources, both financial and personnel. Regarding secondary prevention, research is needed to determi-

ne how an optimal provision of prenatal diagnosis and use of services may be achieved. Health personnel who work in the field of reproductive health should study ways to decrease the risk factors causing neural tube defects and make the population aware of this concept.

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