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Retrospective evaluation and one year monitoring of 58 patients according to neural tube defect etiology

Retrospektivní hodnocení a jednoleté sledování 58 pacientů podle etiologie defektu nervové trubice

Abstract

Aim: Neural tube defects (NTDs) are a group of diseases caused by genetic and environmental factors; however, their complete etiology remains unknown. Folate deficiency, medications, maternal diseases and a low socioeconomic status, as well as genetic factors, are known risk factors for NTD. The purpose of this study was to determine possible etiologic factors of NTD and to evaluate patients after 1 year of monitoring. *Methods:* We retrospectively analyzed 58 patients who were operated as neonates at our hospital in 2017. *Results:* Of 58 patients, 60.3% were female and 39.7% were male. The frequency of birth abnormalities was higher in mothers aged > 35 years. Overall, 56.9% of the pregnancies occurred during the hot months and 43.1% during the cold months according to the neurulation period. Encephalocele was detected in 3.4%, myelomeningocele in 31% and myeloschisis in 63.8% of patients. Of all patients, 60.3% were diagnosed with hydrocephalus either at birth or at a 1-year follow-up, and they wore a shunt. *Conclusion:* The results indicate that NTD incidence is higher among females and exerts a high myeloschisis frequency. Other risk factors include kin marriage, family history of NTD, a maternal age outside the range of 19–34 years and mothers with 0 Rh+ blood type. Furthermore, there was a high incidence of abnormalities in the urinary and other systems, which should be considered during patients' monitoring and surgery. Additionally, there may be a correlation between a sac size and hydrocephalus as well as between myeloschisis and a risk of hydrocephalus.

Souhrn

Cíl: Defekty nervové trubice (neural tube defects, NTD) jsou skupina onemocnění vyvolaných genetickými a environmentálními faktory; jejich kompletní etiologie ale zůstává neznámá. Mezi známé rizikové faktory NTD patří nedostatek kyseliny listové, některé léky, onemocnění matky, nízká socioekonomická úroveň a genetické faktory. Účelem této studie bylo stanovit možné etiologické faktory NTD a zhodnotit pacienty po 1 roce sledování. *Metody:* Retrospektivně jsme analyzovali 58 pacientů, kteří byli jako novorozenci operováni v naší nemocnici v roce 2017. *Výsledky:* Z 58 pacientů bylo 60,3 % dívek a 39,7 % chlapců. Frekvence výskytu vrozených vad byla vyšší u matek ve věku > 35 let. Podle období vývoje neuruly vzniklo 56,9 % těhotenství v teplých měsících a 43,1 % ve studených měsících roku. Encefalokéla byla zjištěna u 3,4 %, myelomeningokéla u 31 % a myeloschiza u 63,8 % pacientů. Ze všech pacientů byl při narození nebo během jednoletého sledování u 60,3 % diagnostikován hydrocefalus; těmto pacientům byl zaveden shunt. *Závěr:* Výsledky svědčí o tom, že incidence NTD je celkově vyšší u dívek a je u nich vyšší výskyt myeloschizy. Mezi ostatní rizikové faktory paří manželství příbuzných osob, NTD v rodinné anamnéze, věk matky mimo rozpětí 19–34 let a matky s krevní skupinou 0 Rh+. Byl také zaznamenán vysoký výskyt abnormalit močového traktu i jiných ústrojí, což by při sledování a operacích těchto pacientů mělo být bráno v úvahu. Navíc pravděpodobně existuje souvislost mezi velikostí vaku a hydrocefalem, a také mezi myeloschizou a rizikem hydrocefalu.

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Introduction

One in every 33 babies is born with a congenital anomaly. Not all congenital anomalies can be prevented; however, precautions can be taken to increase the chances of delivering a healthy baby [1,2]. Neural tube defects (NTDs) are congenital anomalies with an incidence of 1/2,858 live births [1]. The etiology of NTDs is not fully known, although genetic and environmental factors are suspected to play a role. Therefore, it is believed that its incidence can be reduced by taking certain protective measures [3,4].

The purpose of this study was to understand the etiological factors causing NTDs. To detect preventable causes of the disease, we retrospectively analyzed patients who were operated at the neonatal unit of our hospital and followed up for 1 year.

Materials and methods

We retrospectively evaluated 58 patients who were either born at the Health Sciences University, Gazi Yasargil Education and Research Hospital, Diyarbakır, Turkey or referred to our hospital and operated in 2017.

The patients were evaluated based on the neurulation month and heat relation, pregnancy count of mother, maternal disease history, medication or smoking history of mother during pregnancy, parents' age, folic acid usage, intermarriage and family history.

The patients whose morbidities and survey results were examined at a 1-year follow-up were evaluated on the base of NTDs type, sex, birth week, birth type, infant blood type, neurological condition, extremity deformation, existence of kidney or other pathologies, location and extension of the pathologies, flap necessity, existence of contusion spot problem and hydrocephalus.

Statistical analysis

The bivariate correlation tests (Pearson's R and Spearman's tests) were used to evaluate the correlation between various parameters. The chi-square test was used to analyze the categorical data. SPSS for Windows (version 20.0) (IBM, Armonk, NY, USA) was used for the analysis. P-values < 0.05 were deemed significant.

Results

Fifty-eight patients who were followed up in the neonatal unit of our hospital in 2017 and operated by the same surgeon at the same hospital were included in the study.

Of 58 patients, 60.3% were female and 39.7% were male. One of the patients with ambiguous genitalia was considered a male infant because he had an XY chromosomal structure. Furthermore, 37.9% of patients were born pre-term (after < 38 weeks), whereas 62.1% were delivered full-term (after 38–41 weeks). Caesarean delivery was performed in 81% of patients, whereas 19% were born by normal spontaneous vaginal birth. In 22.4% of cases, the parents were relatives. The ratio of patients with a family history was 12.1%.

Overall, 10.7% of patients were primipara, 44.6% were multipara and 44.6% were grand multipara. The youngest mother in the study was 18 years and the oldest was 41 years old. The average maternal age was 29.9 years. Furthermore, 5.2% of mothers were ≤ 18 years, 39% were 19–24 years, 24.7% were 25–34 years and 31% were > 34 years old. The frequency of birth abnormalities was higher in mothers aged > 35 years.

The youngest father in our study was 17 years, whereas the oldest was 45 years old. Overall, 50.9% of the fathers of infants with NTDs were ≤ 35 years, whereas 49.1% were > 35 years old.

In this study, 39.7% of mothers had 0 Rh+, 29.3% A Rh+, 13.8% B Rh+, 5.2% AB Rh+, 5.2% A Rh–, 3.4% B Rh–, and 1.7% had 0 Rh– and AB Rh– blood types. When the Rh groups alone were compared, 91.4% of mothers had an Rh+ blood type. This data is consistent with the blood type variance research. Also, 39.7% of the infants with NTD had A Rh+, 31.1% 0 Rh+, 17.2% B Rh+, 5.2% 0 Rh–, 3.4% A Rh– and 3.4% had AB Rh+ blood types. Overall, 91.4% of the infants had Rh+ and 8.6% had Rh– blood types.

Five (8.6%) of the mothers had a known history of arterial hypertension, and one of them developed preeclampsia. The other four mothers received regular antihypertensive treatment (methyldopa). One of the mothers had Hashimoto's thyroiditis and was treated with levothyroxine sodium. None of the other mothers received regular medication. Four (6.9%) of the mothers had a history of smoking during pregnancy but none had a history of alcohol usage.

Birth rates by month were as follows: 8.62% in January, 3.45% in February, 10.34% in March, 12.07% in April, 6.9% in May, 8.62% in June, 12.07% in July, 6.9% in August, 10.34% in September, 6.9% in October, 5.17% in November and 8.62% in December. The months that have an average (room) temperature of 24 °C and at least 12 h of daylight per day were termed as hot months. These months include those from April to September. The rest, from October to March, were termed as cold months. Thus, 56.9% of the pregnancies occurred during the hot months and 43.1% during the cold months according to the neurulation period. When neurulation coincided with hot months, the NTD rates increased, but the increase was not significant.

Encephalocele was detected in 3.4%, myelomeningocele in 31% and myeloschisis in 63.8% of patients. There was one incident of encephalocele + myeloschisis and another incident of two myelomeningocele sacs. Out of all patients, 6.9% had 4–5/5 muscle power in their lower extremities, 17.2% had paresis, 75.9% had plegia and 65.5% had deformities in their extremities.

The sac was detected in the lumbar area in 44.9%, in the lumbosacral area in 5.2%, in the thoracic area in 5.2%, in the thoracolumbar area in 37.9% and in the occipital area in 3.4% of patients. In addition, two sacs were detected in the occipital and lumbar areas in one patient (1.7%) and in the thoracic and thoracolumbar joints in another patient (1.7%).

The sacs smaller than or equal 25 cm^2 were detected in 24.1% of patients, whereas 79.9% had sacs larger than 25 cm^2. The smallest sac measured 2 cm^2, whereas the largest one measured 150 cm^2. Two (3.4%) patients needed a flap during the first surgery. One patient developed wound necrosis at the first surgery without a flap but later recovered after the second operation.

Of all patients, 48.3% had anomalies from the central nervous system and kidneys. More than two systems were affected in 8.6% of patients. One of the patients had Meckel-Gruber syndrome. Seven patients had cardiac abnormalities (1× ductus arteriosus, 1× foramen ovale, 1× ventricular septal defect, 2× secundum atrial septal defect, 2× secundum atrial septal defect + patent ductus arteriosus), one patient had facial abnormality (cleft palate and lips), four patients had gastrointestinal system abnormalities (1× duodenal atresia, 2× ileal atresia and 1× esophageal atresia), two patients had genitourinary system abnormalities (1× inguinal hernia and 1× ambiguous genitalia) and three patients had extremity abnormalities other than club-foot (1× achondroplasia, 1× polydactyly and 1× syndactyly).

Of the 19% patients with congenital urinary system abnormalities, seven had hyd-

ronephrosis from birth, three had single kidney agenesis and one had polycystic kidney disease.

Five (8.5%) of the patients developed neurogenic bladder and had to use clean intermittent catheterization during a 1-year follow-up.

Of all patients, 60.3% were diagnosed with hydrocephalus either at birth or at a 1-year follow-up, and they wore a shunt; 38.9% of patients with myelomeningocele and 70.3% of those with myeloschisis had hydrocephalus. These differences were significant ($P = 0.02$).

Of all patients with myelomeningocele, 50% had abnormalities in various systems besides the urinary system, and 43.2% of patients with myeloschisis had these abnormalities, although the difference was not significant ($P > 0.05$).

Of all the patients who wore a shunt because of hydrocephalus, 37.1% were male and 62.9% were female ($P > 0.05$).

Of all the patients who wore a shunt because of hydrocephalus 34.3% were born preterm, whereas 65.7% were full-term; 54% of the preterm patients had hydrocephalus compared with 65% full-term patients ($P > 0.05$).

Of all patients who wore a shunt because of hydrocephalus, 60% were infants with neurulation during hot months compared with 40% with neurulation in cold months ($P > 0.05$); 83% of the patients with primipara pregnancy had hydrocephalus compared with 52% with multipara pregnancy and 64% with grand multipara pregnancy ($P > 0.05$). Furthermore, 80% of the infants with hydrocephalus were delivered through the Caesarean section.

Of all the patients with a flap size < 25 cm^2, 35% had hydrocephalus, compared with 75% of the patients with a flap size > 25 cm^2 with hydrocephalus ($P = 0.031$).

In the 94.8% patients who were discharged from the hospital, no mortality occurred during a 1-year follow-up. Mortality occurred in three (5.2%) patients, two of whom died at the neonatal unit; the other one died at 5 months.

Discussion

Neural tube defects are the most frequent and the most tragic congenital abnormalities of the central nervous system [5]. NTDs, which are caused by abnormal neurulation, need further research because their etiology is multifactorial [5,6].

The brain and spinal cord develop between the 15th and 28th days after conception. This process, named neurulation, is a crucial period in which NTDs may develop. Cranial neuropore defects are named anencephaly/encephalocele, whereas caudal neuropore defects are named spinal dysraphism [5,6]. In our study, the neurulation period (15th–28th days) was estimated based on the birth date and birth week (birth date – birth week + 15th day and 28th day). In 2017 at Diyarbakir, the months between April and September were termed hot months; the months between October and March were termed cold months. Meteorological data were collected from the Agriculture and Forest Ministry of Turkey to determine the weather data of Diyarbakir in 2017. We found that for 56.9% of pregnancies, the neurulation period was during hot months, whereas for 43.1% of pregnancies it was during the cold months. Although there was an increase in the incidence of NTDs in the hot months, the differences were not statistically significant. Animal experiments have shown that hyperthermia affects neural tube development [7]; however, the study done by Auger et al. proves that the relationship between hot weather and NTDs is weak [8], which is supported by our results. The present study results support the thesis that hot weather conditions do not affect NTDs at the 3rd and 4th week after conception. However, other heat-induced effects (hot showers, diseases that cause hyperthermia, etc.), which the mother may be exposed to, should be studied further.

NTDs are classified as anterior neuropore (anencephaly/encephalocele) and posterior neuropore (spina bifida) development disorders. Based on its appearance, spina bifida is classified into two subcategories: spina bifida aperta and spina bifida occulta [1,6,9]. In our study, 3.4% of patients had encephalocele, whereas 31% had meningomyelocele and 63.8% had myleoschisis. One of the patients had encephalocele + myeloschisis, whereas another had two myelomeningocele sacs. Myeloschisis, a developmental disorder that occurs as a result of the earliest embryological effect, did not have neurulation and the neural plaque was steady as it was. It is mostly observed in the thoracolumbar area. In the myelomeningocele case, there was an unidentified neurulation defection and a sac in the dorsal area with neural elements inside. This is mostly observed in the lumbar, lumbosacral and sacral areas [10]. Of all patients with myelomeningocele, 55.5% had sacs in the lumbar area; 45.9% of patients with myeloschisis had sacs in the lumbar area, and 43.2% of them had sacs in the thoracolumbar area. The data on myelomeningocele are consistent with the literature, whereas myeloschisis data in the literature show sacs to be present more often around the lumbar and thoracolumbar areas.

There was female dominancy at about 61.8% in three studies, with 2,133 cases reported by Poletta et al., which is consistent with our results of 3/2 female dominancy [11].

The frequency of NTDs is one in every 2,858 live births [11]. In our study, the ratio was 1.7/1,000. Most (62.1%) of the patients in our study were term infants born through the Caesarean section (81%). Almost half (44.6%) of the pregnancies were grand multipara. Although Nasri set mother parity as one or more, he declared that an increase in gravida number is a risk factor for NTDs development, which is in agreement with our results [9].

Dupepe et al. reported that there is a 16.9% risk of NTD in the presence of family history [12]. Our study, in which first- and second-level NTDs patients were taken into account, showed a risk of 12.1% for family history; 22.4% of the parents were kin. The risk of NTDs in infants increases with family history of NTDs and a kin marriage [5,9,12].

According to the World Health Organization data, the maternal age for a healthy pregnancy is 19–34 years. The total number of births in Diyarbakir in 2017 was 39,576; of them, 650 (1.6%) mothers were < 18 years, 12,203 (30.8%) were 19–25 years, 20,408 (51.5%) were 25–34 years and 6,315 (15.9%) were > 34 years old (data from Diyarbakir Health Department database). According to Vieria and Taucher, there is a U-shaped relationship between mother's age and NTDs [13]. Our study indicates a similar outcome, suggesting that NTDs risk increases when the mother's age is < 18 and > 34 years, whereas it decreases in mothers aged 19–34 years.

In our study, 52.6% fathers of the infants with NTDs were < 35 years, whereas 49.1% were > 35 years old. The average age ratio of the fathers in Diyarbakir city in 2017 was not known. Nonetheless, assuming that the age of the fathers was similar to that of the mothers, it may be estimated that infants with fathers aged > 35 years are at a higher risk for developing NTDs. Nevertheless, further investigation is needed to determine whe-

ther NTDs risk is conferred by the mother's or father's age.

In this study, 3.4% of mothers had planned pregnancy and started to use folic acid 2 months before conception. On the other hand, 5.1% of the pregnancies were not monitored and, therefore, lacked folic acid use or any multivitamin support. The rest of the mothers started to use folic acid after pregnancy detection. Previous studies have reported that folic acid use before conception decreases the incidence of NTDs. However, folic acid support alone is not able to prevent the occurrence of NTDs.

Regarding the blood type of mothers, it was observed that 39.6% were 0 Rh+. In the study conducted by Temiz et al., of 206,673 participants from Diyarbakır city 36.55% were A Rh+, 29.7% 0 Rh+, 16.65% B Rh+, 6.26% AB Rh+, 4.26% A Rh–, 3.95% 0 Rh–, 1.88% B Rh– and 0.72% were AB Rh–. Furthermore, the participants included in the study had 89.17% Rh positivity and 10.82% Rh negativity [14]. In our study, it was observed that the risk of giving birth to an infant with NTD was significantly higher among mothers with 0 Rh+ blood type than among those with A Rh+ blood type and was relatively similar among mothers with B Rh+, AB Rh+, A Rh– and 0 Rh– blood types. The study lacked B Rh– and AB Rh– blood type mothers, which is normal, considering the ratio of patient number and blood types. The study by Nasri et al. indicates that the chance of giving birth to an infant with NTD increases if the mother has 0 Rh+ blood type [9]. Because our study corroborates this result, it necessitates further investigation about whether this blood type has an effect on NTDs development. The distribution of Rh groups in our study was similar to that in the data of Diyarbakir society; also, the data for blood type of infants with NTDs were similar to the data of Diyarbakir society [14].

Four (6.9%) of the mothers in our study had a history of smoking during pregnancy, but none of them had a history of alcohol use. Ryznychuk et al. emphasized that smoking during pregnancy is a potential risk factor for NTDs development [15].

Although several studies have been conducted on the etiology of NTDs, their underlying mechanisms remain unclear. One of the patients in our study has a twin, who is a healthy infant. As in the previous studies, this outcome indicates that NTDs etiopathogenesis is complicated and genetic or environmental factors alone cannot be blamed. However, it is necessary to take precautions against possible etiology, and further investigate the etiopathogenesis of NTDs.

Babies born with open NTDs usually survive with appropriate medical care but suffer from neurological impairment, the severity of which depends on the level of the lesion. Associated conditions include hydrocephalus, Chiari malformation type II and vertebral abnormalities as well as genitourinary and gastrointestinal disorders [16].

The patients in our study had impaired muscle function in their extremities. Club-foot was detected in 65.5% of patients.

Central nervous system and extra-renal abnormalities were present in 48.3% of patients. Based on the data from the Centers for Disease Control and Prevention, the incidence of additional diseases in our patients was as follows: atrial septal defect, 1/2,122; ventricular septal defect, 42/10,000; cleft palate, 1/940; esophagus atresia, 1/4,608; intestinal atresia, 1/2,108 and lower extremity abnormality (besides club-foot), 1/5,949. There were other congenital abnormalities besides NTDs and related diseases (urinary system abnormalities and club-foot) in almost half of our patients, which indicates that the risk of additional abnormality development is high in patients with NTDs. This situation points out that screenings for other systems should be performed and comorbidities should be considered during surgery planning for patients with NTDs [16].

Of our patients, 19% had accompanied congenital urinary system abnormalities. One-sided renal agenesis was detected in 3 of 286 spina bifida patients in a study conducted by Torre et al. Our study has a similar outcome of three patients with single kidney agenesis. Renal problems in NTDs patients present difficulties both during surgery and patient monitoring, contributing to increased morbidity [17].

Shunts were inserted in 60.3% of patients after the diagnosis of hydrocephalus at birth or during monitoring. Significantly higher level of hydrocephalus development was observed in patients with myeloschisis than in patients with myelomeningocele. An increased head circumference and fontanelle tension is important for shunt requirement [18]. This highlights the importance of close monitoring of these patients for hydrocephalus development so that the number of the patients dependent on shunts can be reduced based on the absence of distinct macrocephalus and/or fontanelle tension at the neural tissue in an intact sac.

While hydrocephalus development was present in 35% of patients with sac size ≤ 25 cm^2, this proportion was 75% in patients with sack size > 25 cm^2; the difference was significant. The sac size increase is considered an important risk factor for hydrocephalus development in NTDs patients.

Neural tube defects are a complex disease group for patients and relatives to bear as well as for doctors to treat. NTDs are associated with high morbidity and mortality rates; thus, their etiopathogenesis needs to be further investigated and explained. The patients profiled in our study were of low socioeconomic status with a high number of early age, short-term and frequent pregnancies, as well as low termination options, a short time of convalescence for the mother and a higher ratio of other congenital diseases. In this study, patients with NTDs were analyzed and evaluated according to regional differences.

Conclusion

The results indicate that NTDs incidence is higher among females. The most common type of NTD in infants is myeloschisis. Other risk factors include kin marriage, family history of NTDs, maternal age outside the range of 19–34 years and mothers with 0 Rh+ blood type. Furthermore, there was a high incidence of abnormalities in the urinary and other systems, which should be considered during patients' monitoring and surgery. Additionally, there may be a correlation between the sac size and hydrocephalus as well as between myeloschisis and the risk for hydrocephalus development.

Ethical aspects

The entire study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2004 and 2008). The study was approved by the Health Science University, Gazi Yasargil Education and Research Hospital Ethics Committee Ethics Committee approval was obtained for this protocol 67, on 13. 4. 2018. Informed consent was obtained from all patients.

Conflict of interest

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

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