Experience of a tertiary care center on 100 newborns with neural tube defects

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The aim of this study was to analyze the sociodemographic features, postoperative complications, long-term problems, and cost of care of patients followed in the neonatal intensive care unit (NICU) with a diagnosis of neural tube defects (NTDs).

Babies with NTD followed in the Neonatology Unit of Ondokuz Mayıs University Faculty of Medicine between January 2003 and December 2011 were analyzed retrospectively.

One hundred (1.2%) of 8408 babies admitted to the NICU were diagnosed as NTD during the study period. Of the cases with NTD, 74% of mothers were graduates of primary school/illiterate, and none had used folic acid (FA) preconceptionally. Prenatal diagnosis was made in 72%, but parents had chosen not to terminate the pregnancy. The most frequent type and site of NTD was meningomyelocele (82%) of the lumbosacral region (36%). In 80% of the babies, the NTD sac was closed within the first 72 hours of life. The most frequently observed postoperative complications were wound infection and septicemia. The mortality rate of babies 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 had neurologic deficits on follow-up. Patients were rehospitalized during the follow-up for an average of 2.9 times.

Neural tube defect (NTD) is a disabling problem, with operations, rehospitalizations and other costly treatments. Maternal education regarding preconceptional FA use/fortification of food with FA and appropriate guidance to the family with prenatal diagnosis will decrease the incidence and burden of the disease.

***Key words:** neural tube defect, newborn, folic acid, operation, complication, cost.*

Neural tube defects (NTDs) are one of the most common forms of human congenital malformations. NTDs occur in 1-6.5 per 1,000 births, with marked geographic and ethnic variations. Comparatively, the incidence of NTD, at 9.5/1,000 births in our region, is somewhat high[1]. While the incidence of meningomyelocele was 6/1,000 live births in the United Kingdom in 1960, with preconceptional folic acid (FA) use and prenatal diagnosis of the disease, the incidence decreased to 1/1,000 live births. The mechanism of preconceptional FA use to decrease NTDs is not clear, but it decreases NTDs by 60-70%[2].

The neural tube closes in the 3rd week of intrauterine life. If it does not close, congenital abnormalities such as encephalocele, anencephaly, meningomyelocele, and myelocele develop[3,4]. The etiology of NTD is multifactorial, with both environmental and genetic factors having a role. In a family with a child with NTD, the risk of NTD for the next child increases to 2-3%[5]. Race, geography, socioeconomic status, nutrition, vitamin deficiencies, and antiepileptic drugs (valproic acid, carbamazepine) are the cited environmental factors[6,7]. Maternal diabetes has also been shown to increase the risk for NTD at least three-fold[8]. Deficiencies of maternal FA, zinc, selenium, and methionine also have a role in the development of NTDs[1,9-11]. According to observational studies, the United States (US) Public Health Service had recommended in 1992 that all pregnant women should take FA as 400 μg/day three months before pregnancy and continue during the first trimester[12]. Although intrauterine treatment is available in some expert clinics[13], in our country, the sac is closed after birth, and if necessary, ventriculoperitoneal shunt is applied.

Patients with NTD can face long-term problems like musculoskeletal deformities, loss of strength, loss of sense, hydrocephalus, shunt infection, shunt dysfunction, neurogenic bladder, and progressive neurologic problems. These problems lead to both moral and financial burden.

The aim of this study was to analyze the sociodemographic features, operation complications, long-term problems, and cost of care of patients followed in the neonatal intensive care unit (NICU) with a diagnosis of NTD.

Material and Methods

Babies with NTD followed in the NICU of Ondokuz Mayıs University Faculty of Medicine between January 2003 and December 2011 were analyzed retrospectively. Perinatal data (sex, delivery mode, gestational age, head circumference, birth weight), maternal features (age, education, FA use, diabetes mellitus, obesity, systemic disease), consanguinity, prenatal diagnosis, features of the sac (location, size, ruptured or not), prophylactic antibiotic use, type of NTD, operation time, postoperative complications (apnea, need for mechanical ventilation, wound infection, septicemia), shunt features (shunt presence, application time, shunt infection, shunt dysfunction), hospitalization frequency and duration, associated abnormalities, and costs incurred for each baby were recorded by using the NICU database. Surface area of the sac was calculated by the formula: Width x Length x д/4. Patients with NTD were followed both pre- and postoperatively in the NICU. If the NTD sac was open, prophylactic ampicillin and netilmicin were ordered according to NICU protocol and continued 24 hours postoperatively.

Data after discharge were obtained from patient files and via phone calls by one of the investigators (SV).

Hospitalization frequency was calculated as every hospital admission. Total hospitalization time was calculated as the sum of the length of hospital stay during each admission. Frequency of hospitalization was documented as between the date of birth to December 2011. Hospitalization cost was calculated as the sum of the cost of the stay for each admission. The local ethics committee approved the study (No: 2010/456). The Statistical Package for the Social Sciences (SPSS) 19.0 computer program was used for statistical analysis. Data were expressed in number, percent, mean and standard deviation. Categorical data were analyzed by chi-square. A p value <0.05 was taken as statistically significant.

Results

One hundred (1.2%) of 8,408 babies admitted to the NICU were diagnosed as NTD. Mean birth weight, gestational age and head circumference of the babies were 2.981.8±574.5 (1430- 4280) g, 38.8±2.2 (29-43) weeks and 35.8±2.9 (28.5-49.5) cm, respectively. Other demographic features are listed in Table I.

The mean age of mothers was 27±6.1 (21-41) years. When maternal education status was questioned, it was observed that 71% had graduated primary school, 12% elementary school, 11% high school, and 3% university; 3% were illiterate. Overall, three-fourths of mothers were either primary school graduates or illiterate.

Mothers were queried regarding FA use after excluding cases with encephaloceles (92 mothers). 82.6% of the mothers had never used FA (76/92, Table I). The mothers reported that they started using FA during the first trimester, after the pregnancy was confirmed. None of them had used FA preconceptionally.

When 16 mothers who had used FA in the first trimester were analyzed, it was observed that first trimester FA use was present in 7.0% of primary school graduates and 100% of university graduates. None of the illiterate mothers had used FA. When the relation between maternal

Table I. Demographic Features of Patients Included in the Study

		Frequency
Sex	Male	39
	Female	61
	Total	100
Delivery mode	Cesarean	74
	Vaginal	26
	Total	100
Consanguinity	(-)	91
	(+)	9
	Total	100
Prenatal diagnosis	(-)	28
	(+)	72
	Total	100
Folic acid use*	(-)	76
	(+)	16
	Total	92
Associated anomalies	Chiari type 1	2
	Chiari type 2	47
	Rib anomaly	3
	Orthopedic problems	54
Hydrocephalus	(+)	67
	(-)	33
	Total	100

*: Mothers were queried regarding folic acid use after excluding cases with encephaloceles.

education and FA use was analyzed, FA use was found to be higher in the mothers who graduated from university (although they had not used it preconceptionally) ($p=0.01$).

When prenatal history was sought, 2 (2%) mothers had diabetes mellitus, 2 (2%) chronic hypertension, 1 (1%) gestational hypertension, 1 (1%) familial Mediterranean fever, and 4 (4%) thyroid problems.

Termination was offered to 72% of the prenatally diagnosed cases, but none of the families accepted. According to maternal education, prenatal diagnosis was present in 67.6% of primary school graduates, 75% of elementary school graduates, 90.9% of high school graduates, 66.7% of university graduates, and 100% of illiterate mothers. There was no statistically significant difference between prenatal diagnosis of NTDs and maternal educational status ($p>0.05$).

The most frequent location of the NTD sac was the lumbosacral region (36%). Thirty percent of sacs were located in the lumbar, 18% in thoracolumbar, 6% in thoracal, 5% in occipital, 2% in cervical, 1% in parietooccipital, 1% in frontal, and 1% in cervicothoracic regions.

Of all patients, 82% were diagnosed as meningomyelocele, 8% as encephalocele, 3% as meningocele, 4% as Jarcho-Levin syndrome, 2% as lipomeningomyelocele, and 1% as lipomeningocele by physical examination and neuroradiological imaging studies (cranial and/or spinal computerized tomography/magnetic resonance imaging).

Mean sac surface area was calculated as 17.7 ± 19.3 cm^2 (2.3-117).

Sac excision was performed in 93% of patients. The operation could not be performed in 7 (7%) babies: 4 (4%) families rejected the operation

Table II. Hospitalization Frequency, Length of Stay and Cost of Care of the NTD Patients

	Hospitalization frequency (n)	Total length of stay (day)	Total cost ($)
Mean	2.9	36.0	7.880
Std. deviation	4.5	40.9	12.680
Minimum	1.0	1.0	100.4
Maximum	43.0	213.0	84.302

and 3 (3%) babies died in the first day of life. The operation was performed in the first 24 hours in 43%, and 80% of patients were operated in the first 72 hours of life. Mean operation time was within 8±21.2 (1-120) days. Eighty percent of all NTD cases were given prophylactic antibiotic before the operation. All patients left the surgery room conscious, but 16% required endotracheal intubation and mechanical ventilation due to postoperative apnea. Postoperative complications were observed in 50% of babies, and the most frequent complications were wound infection (21%) and septicemia (17%). There was no statistically significant relation between sac surface area and wound infection ($p=0.35$).

Hydrocephalus was associated in 67%, and of these, ventriculoperitoneal (VP) shunt was applied to 59 babies (88%). Mean shunt application time was within 17±26.4 (1-150) days. Shunt infection, shunt dysfunction or both were diagnosed in 27 (45%), 26 (44%) and 18 (30%) of VP shunts, respectively.

Neurological deficits (loss of strength, loss of sense, fecal incontinence, and neurogenic bladder) were observed in 62% of babies. Orthopedic malformations were determined in 54% of patients as associated problems. The most frequently observed orthopedic malformation was pes equinovarus (32%).

Bladder dysfunction was diagnosed in 42% of patients. Other observed urological problems were: globe vesicale in 19%, neurogenic bladder in 17% and vesicoureteral reflux in 6% of patients.

Hospitalization frequency, total length of stay and total cost of all hospitalizations within these nine years are shown in Table II. The most common time of admission was within the first six months.

Seven percent of babies died during the study period. Two (28.6%) babies died due to severe malformations and respiratory insufficiency due to Jarcho-Levin syndrome. The others died due to aspiration and chocking. All deaths occurred within the first year of life. Follow-up of the patients began from birth and is continuing.

Discussion

Prevalence of NTDs had decreased with preconceptional FA use in developed countries, but NTD remains an important health problem in developing and underdeveloped countries[14]. The first distractive result in our study was that 72% of patients were diagnosed prenatally, and none of the families had accepted the termination despite consultations to gynecologists, neonatologists and neurosurgeons. Continuation of pregnancy is common in traditional societies even among parents who are counselled about the abnormalities and high lethality of the conditions. Similar to our results, in the study by Bulbul et al.[14] from Turkey, it was reported that families rejected termination even though three-fourths had been diagnosed prenatally as having NTD. Patients with NTD encounter problems not only in their NICU stay, but also incur recurrent hospitalizations in the long-term follow-up. The mean hospitalization number was calculated as 2.9 in the study period. This number peaked to 43 for some babies. When calculating the rehospitalization frequency, only the admissions within the study period of nine years were included. It can easily be expected that rehospitalization frequency will increase as the babies continue to grow. Total mean hospitalization cost was 7,880 USD, and this will also increase with recurrent hospital admissions. The most costly period was the first hospital stay. When calculating the cost, we only took into consideration the hospitalization charges. The cost will surely increase if travel expenses of the families, costs of outpatient clinics for those babies and labor loss of parents are taken into account. It had been calculated that a baby with NTD in the US costs 1.4 million dollars over a 20-year follow-up[15]. Costs are not as high as in the US, but it is a considerable situation for our country.

The data about complications after NTD closure are limited. In the present study, the most frequent complication in the early postoperative period was apnea. Postoperative apnea has been reported to be rare in term infants[16]. In our series, postoperative apnea requiring mechanical ventilation was observed in one out of six babies in whom the sac was closed, so the NICU should be ready to mechanically ventilate the baby.

Folic acid (FA) use was reported as 17.4% in the present study. In many countries, women are encouraged to take FA-containing food and 400 μg/day FA at least one month before pregnancy and to continue taking it for three months following conception since it was shown that FA replacement decreases the incidence of NTD. The reported decrement rate of NTD was 19% in the US and 46% in Canada after enrichment of foods with FA[17]. It is known that NTD prevalence decreased with an increase in prenatal diagnostic facilities and encouragement of using FA as a health policy in European countries, the US and Canada[18]. Policies about preconceptional FA use should also be encouraged since NTD prevalence is high in our country.

The importance of maternal education on the development of NTD was stressed in former studies[19]. In accordance with those results, three-fourths of mothers of NTD patients in the present study were either primary school graduates or illiterates. FA use was inversely proportional with maternal education. This condition shows that uneducated mothers have a higher risk of giving birth to a baby with NTD. Educational programs to decrease NTD should be especially targeted to this population, and the information should be presented in a simple and understandable manner.

In our study, 43% of babies were operated in the first 24 hours and 80% were operated in the first 72 hours of life. The ideal time for meningomyelocele operation is within 48 hours of birth. It is recommended that the sac should be closed in the first 24-48 hours to decrease the risk of infection[20,21]. The mortality rate among babies during the first six months who had not been operated was 65-75%[21]. Babies who had been operated have a mortality rate of 30-40% up to the end of the first year, and the mortality is 50-60% at 3-5 years of age. Reasons for mortality differ from country to country. Postoperative intracranial infections were reported as the most frequent cause of mortality in Nigeria[22]. The mortality rate was 7% in our study, and the cause of mortality was not infection, but either congenital malformations like Jarcho-Levin syndrome or aspiration at home. The reason for the low mortality in our study can be attributed to the admissions of the babies to the NICU postoperatively, where mechanical ventilation and other modalities of critical care are available. It was previously shown that the ventriculitis rate was 7% if the was baby operated in the first 48 hours, but the rate increases to 37% if the operation is delayed after 48 hours[21].

Wound infection was reported at rates of 1-1.5% and 7% in different studies[23,24]. The rate of wound infection was 21% in our study. The rate might be high due to the relatively late sac closure operations.

Neural tube defect (NTD) is an important problem in our country. It has been known for 40 years that NTD is a preventable problem, but public information is lacking regarding NTDs. Educating women and informing fertile women about preconceptional FA use or fortification of food seem to be the key points[25,26]. Rouhani et al.[27] reported in 2001 from Spain that if all women could reach foods that were enriched with FA, then socioeconomic status would become a negligible risk factor for NTD development. Food fortification seems easier than educating fertile women. Prenatal diagnosis is also very important, but the tendency of the families to reject termination due to social/religious beliefs limits the benefits of the prenatal work-up. After birth, the operation should be performed as soon as possible with cooperation of neurosurgeons and neonatologists, which will decrease mortality and postoperative complications.

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