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The effect of defect size on mortality and morbidity in patients with neural tube defect

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Abstract

Aim: Neural tube defects (NTD) occur due to errors in the closing of neural canal in embryo. All over the world, the incidence of all forms of NTD varies between 1.4 and 2 in every 1000 live births. The aim of the present study was to investigate the short term prognosis, accompanying anomalies and complications in patients with NTD and to evaluate the relation between defect sizes.
Material and Methods: Patients who applied to Inonu University Neonatology Department between January 2010 and December 2017 with the diagnosis of NTD and were operated on were included in the study. Babies who died within the first 24 hours were excluded from the study. Patients were divided into two groups according to the size of NTD; < 5 cm (Group 1) and ≥ 5 cm (Group 2). Approval for the study was obtained from local ethics committee.
Results: Overall 133 infants were included in the study. Mean birth weight was 3155 ± 531 g and mean duration of pregnancy was on 38.1 ± 1.8 weeks. Of NTD's 82% was located in lumbosacral region. 90.2% of the patients underwent operation within the first 24 hours. Parameters such as hydrocephalus, need for shunt, need for flap in tissue defects, the rate of postoperative complications, duration of hospitalization, mortality and the use of antibiotics were found to be at a higher rate in cases whose defect size was ≥5 cm than in those whose defect size was < 5 cm ($p < 0.005$). Postoperative complications developed in 48.1% of the patients. The most common complications were observed to be cerebrospinal fluid (CSF) leakage (24.1%) and bladder dysfunction (7.5%).
Conclusion: In patients with NTD, as the size of the defect increases, additional interventions, complications, hospitalization rates and mortality increase as well. Therefore, it is recommended that health care personnel should take care against problems in the management of this group of patients and inform familes beforehand on these issues.

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Introduction

Neural tube defect (NTD) is the most common of congenital anomalies in central nervous system. It is defined as the posterior closing defect of neural canal developing between first 3rd and 4th weeks of pregnancy. The neural tube fusion starts at the level of the hindbrain (medulla and pons) and progresses rostrally and caudally. Incomplete fusion caudally leads to the formation of meningomyelocele around day 26 of gestation. Although its incidence in our country has been reported to between 3-9 in every 1000 live births, it may vary depending on ethnic origin, region, cultural characteristics and socioeconomic status (1, 2). Females have a 3-7 times higher risk compared to males (2, 3).

Even though early repair of NTD decreases morbidity and mortality, in patients with NTD, complication such as cerebrospinal fluid (CSF) leakage, meningitis, and wound infection occur commonly in post operative period. In addition to early surgical intervention, the size of the defect, accompanying urological and orthopedical anomalies and the presence of seizures are other factors associated with short and long term morbidity (2).

The aim of this retrospective observational study was to investigate the clinical characteristics, short term prognoses, accompanying anomalies and complications of patients admitted to newborn clinic with the diagnosis of NTD and who undergo operation and to evaluate the relation between defect size and short term morbidity.

Materials and Methods

One hundred and thirty-three infants admitted to the newborn clinic of our hospital with the diagnosis of NTD between January 2010- December 2017 were included in the present study. The data of the patients were recorded retrospectively. Weight, head circumference, modes of birth, antenatal diagnoses, the status of consanquine marriage, age of the mother, accompanying anomalies, the presence of hydrocephalus, shunt place-

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ment, localization and size of of the defect, day of operation, the presence of postoperative complications, the number of surgical interventions, duration of antibiotic use (vancomycin or cefotaxime for meningitis/ventriculitis and/or local infection),duration of hospitalization and aditional anomalies were recorded.

Patients were divided into two groups according to the size of the defect: Patients whose defect size was under 5cm were allocated to group 1 and those whose defect size was 5cm or over were allocated into Group 2. Long side of the defect was used to determine defect size. Defect type (meningocele, meningomyelocele, encephalocele) was recorded according to the results of pathological evaluation. Two groups were compared in terms of demographic characteristics and short term morbidity.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Microsoft Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Data were expressed with mean ± standard deviation and number (percentage). Whether data were normally distributed was evaluated using Shapiro-Wilk test. In statistical analyses, where necessary, Mann-Whitney U test, significance of the difference between two means test and chi square tests were used. A p-value of < 0.05 was considered indicative of statistical significance. Approval for the study was obtained from local ethics committee with the number/date of 2018/4-22 / 13.02.2018.

Results

It was established that of 133 patients followed in Newborn Intensive Care Unit with the diagnosis of NTD, only 32.3% was diagnosed in prenatal period. It was also determined that approximately half of the patients. (52.6%) were girls and a large majority (78.2%) was delivered with ceaserian section. Mean birth weight was 3155 ± 531 gram and mean duration of pregnancy was 38.1 ± 1.8 weeks, without any statistically significant difference between two groups ($p > 0.05$) (Table 1).

Mean head circumference was found to be 36.3 ± 4.5 cm without any significant difference between two groups ($p = 0.1$). Hydrocephalus was detected in 60.9% of the patients and its presence was found to be significantly higher in patients in Group 2 (71.6%) than those in Group 1 (50%) ($p = 0.01$). It was also established that ventriculo/peritoneal (V/P) shunt placement was carried out in 59.4% of the patients along with defect repair and that the need for V/P shunt placement was significantly higher in patients in group Group 2 (73.1%) than those in Group 2 (45.5%) ($p = 0.001$) (Table 1).

It was found that 90.2% of the patients underwent operation within the first 24 hours whilst 9% did so on the second day, without any significant difference between two groups in this respect ($p = 0.5$). Flap was required in 15.8% of the patients while their defects were closed. The need for flap was seen at a much higher rate in Group 2 (29.9%) than in Group1 (1.5%). ($p < 0.001$). It was observed that 18% ($n = 24$) of patients required a second operation owing to reasons such as shunt dysfunction and dehiscence of the wound.

In the evaluation of pathology reports, the most commonly occurring defect type was observed to be meningocel (66.2%). A large portion of NTD's (%82) was located in lumbosacral region, without any significant difference between two groups. ($p = 0.2$) (Table 2).

It was found that in follow up period, complication developed in 48.1% of the patients and the rate of complications was significantly higher in Group 2 (68.7%) than that in Group 1 (50%) ($P < 0.01$) (Table 1). The most commonly occurring complications were CSF leakage (24.1%), bladder dysfunction (7.5%), meningitis (6%) and convulsion (6.8%) (Table 2). It was established in follow up period that in 23.5% of patients, treatment was initiated with the diagnosis of hypothyroidism and in long term follow up, 6.8% of the patients were diagnosed with epilepsy. In 34.6% of the patients, other anomalies accompanying NTD's were detected. The most commonly observed anomaly was pes equino varus deformity (%18). In the follow up of patients, it was established that patients in group 2 used antibiotics for a longer period than those in Group1 ($p = 0.007$), and were hospitalized for a longer period ($p = 0.02$). During follow up period, 7 (%5.3) patients, all of whom were in Group 2, died ($P = 0.007$) (Table 1).

Discussion

NTD's are the most commonly occurring congenital anomaly of central nervous system. With the advances in medical technology and the increase in monitorization in prenatal period, the probability of prenatal diagnosis has increased. Most neonates are diagnosed by maternal screening by ultrasound and/or serum levels of alpha-fetoprotein (1). In two studies carried out in Turkey, antenatal diagnosis rate of NTD's were reported to be respectively 71.4% and 72% (3, 4). In the present study, the rate of prenatal diagnosis was found to be 32.3% by ultrasound, which was low compared to other reports in the literature. We believe that this low rate may be attributed to the fact that our patient groups was mostly of rural origin and included pregnant women who were not monitorized closely.

The level of NTD is an important indicator for future lower extremity function and ambulation of the patient. In lesions at higher levels, as loss of innervation will be at a higher degree, marked paraparesia may be seen. Results are as much related to the amount of nerve tissue they contain as to the level of lesion (5). In various studies, the most commonly observed defect level was reported to be lumbal region (84 - 92.9%) (2, 3). Consistent with the literature, in the present study, the rate of defects in lumbal region was found to be 82%. In the evaluation of pathology reports, the most common defect type was established to be meningocele (66.2%).

In patients with NTD, unless central nervous system infection is present, ideal operation time is the first 48 hours. Early surgical intervetion is associated with low mortality and morbidity. According to present data, it has been reported that operation carried out within first 48 hours has no impact on lower extremity paralysis, but decreases the risk of wound infecton and meningitis (4, 6, 7). In addition, early surgical correction has been reported to lead to improvement in lower urinary system functions and to increase in bladder capacity as demonstrated in urodynamic studies (8). In the study of Beuriat et patients underwent meningomyelocele (MMC) closure in the first 48 hours of life (7). While 99.2% of our cases underwent operation within the first 48 hours, 90.2% of these being within the first 48 hours, 90.2% of these were within the first 24 hours in the present study.

In patients with, NTD, hyrdocephalus may develop secondarily to the impairment of CSF circulation. Hydrocephalus may develop in intrauterine period or postnatal follow up (9). In 60.9% of our patients, hydrocephalus was detected at birth and its rate

Table 1. Demographic characteristics and treatment periods of the patients with neural tube defect

	All patients (n = 133)	Group 1 (n = 66)	Group 2 (n = 67)	p-value†
Gender (female), n (%)	70 (52.6)	34 (51.5)	36 (53.7)	0.7
Birth weight, g*	3155 ± 531	3080 ± 537	3228 ± 519	0.1
Gestational weeks*	38.1 ± 1.8	37.8 ± 2.1	38.4 ± 1.5	0.08
Mode of delivery (Caesarean), n (%)	104 (78.2)	53 (80.3)	51 (76.1)	0.5
Maternal age, years*	29.8 ± 6.3	30.4 ± 6.6	29.2 ± 6	0.2
Head circumference, cm*	36.3 ± 4.5	35.7 ± 4.5	36.9 ± 4.5	0.1
Hydrocephalus, n (%)	81 (60.9)	33 (50)	48 (71.6)	0.01
Ventrikülo/Peritoneal şant, n (%)	79 (59.4)	30 (45.5)	49 (73.1)	0.001
Anomaly, n (%)	46 (34.6)	19 (28.7)	27 (40.3)	0.49
Total complications, n (%)	64 (48.1)	18 (50)	46 (68.7)	<0.01
Flap need, n (%)	21 (15.8)	1 (1.5)	20 (29.9)	<0.01
First day operation, n (%)	120 (90.2)	60 (90.9)	60 (89.6)	0.5
Hypothyroid, n (%)	31 (23.5)	13 (19.7)	18 (27.3)	0.4
Duration of antibiotic treatment, days*	11 ± 4.6	9.9 ± 3.8	12 ± 5	0.007
Duration of hospital stay, days*	19.2 ± 10.8	17 ± 9.4	21.3 ± 11.7	0.02
Death, n (%)	7 (5.3)	0 (0)	7 (10.4)	0.007

* Values are given as mean±standard deviation. † Results of statistical comparisons between groups 1 and 2

Table 2. Localization of meningomyelocele, neurological status, complications and additional anomalies of the study population

Defect Type		n (%)
	Meningocele	88 (66.2)
	Meningomyelocele	29 (21.8)
	Encephalocele	16 (12)
Defect Size		
	<5 cm	66 (49.6)
	≥5 cm	67 (50.4)
Defect Localization		
	Occipital	11 (8.3)
	Cervical	7 (5.3)
	Thoracic	6 (4.5)
	Lumbosacral	109 (82)
Complication		
	No complication	69 (51.9)
	Local infection	5 (3.8)
	Meningitis	8 (6)
	Convulsions	9 (6.8)
	Bladder dysfunction	10 (7.5)
	Cerebrospinal fluid leakage	32 (24.1)

was significantly higher in Group 2 (71.6%) than in Group 1 (p = 0.01). There is a direct correlation between the size of the defect and its negative effect on CSF circulation, which may account for this result. Although placements of V/P shunt theoretically increases the risk of infection, it is not considered a major risk factor for infection in recent studies. In a retrospective observational study in which 60 cases, whose median duration of operation was 21 hours, were evaluated, although the rate of wound infection was reported to be 11.7%, the presence of V/P shunt was not found to be associated with infection (6, 10). Since only 5% to 25% of children with MMC present with overt hydrocephalus, the need to perform VP shunting in the same session as MMC repair is questionable (11). Although there is no consensus on the timing of V/P shunt placement together with defect repair, in patients without marked ventriculomegaly and clinical findings of hydrocephalus, the placement of V/P shunt may be delayed (5). In the present study, shunt was placed simultaneously with defect repair in 79 of the 81 patients with hydrocephalus. The need for V/P shunt placement was seen at a higher rate in patients in Group 2 (73.1%) than those in group1 (45.5%) (p = 0.001), since the rate of hydrocephalus was higher in Group 2.

In patients undergoing NTD repair, complications such as local infection, CSF leakage, meningitis and bladder dysfunction may develop postoperatively. In large spinal defects, complications may occur more frequently. Compared to small defects, central nervous system and wound infections occur more commonly in large defects. Moreover, in patients with larger defects, the duration of hospitalization is substantially longer (2). In the study of Oncel et al, complications were reported to develop in 53.3% of patients, the most frequent complication being bladder dysfunction (23.3%) (12). In the present study, complication occurred in 48.1% of patients, being more common in patients in group 2. The most frequently observed complications were CSF leakage (24.1%) and bladder dysfunction (7.5%). Of patients with CSF leakage, 32.2% underwent surgical intervention again. In one study, early surgical revision was required in 12.5% of patients due to delayed wound healing and the cause of CSF fistula (13). In the present study, the rate of meningitis and wound infection were found to be respectively 6.8% and 3.8%, which was considerably low compared to results reported in the literature (2, 14).

The rate of convulsions was found to be 14-30% in patients undergoing postnatal NTD repair. While the rate of convulsion is low in NTP patients without V/P shunt and hydrocephalus, it was found to be high in patients with shunt. High rate of convulsion in patients with shunt may be attributed to cortical damage during shunt placement or especially infectious complications associated with shunt. In addition, convulsions may occur related to the accompanying congenital anomalies of central nervous system (15). In the present study, it was established that % 6.8 of the patients (n = 9) experienced convulsions and of

these patients, 6 were those who were subjected to shunt placement due to hydrocephalus. In long term follow up of these patients, 3 were diagnosed with epilepsy.

In neuromuscular diseases, congenital foot deformities occur commonly. Although pathophysiology of foot deformities in NTD patients remains unclear, it is thought that they develop due to muscular imbalance in intrauterine period, spasticity and and position. The frequency of foot deformities varies depending on the level of lesion and the lower the lesion level, the lower the incidence of deformity. In spina bifida, the rate of foot deformities has been reported to be 9% and 75% respectively (16, 17). In the present study, foot deformity was found to be 18% (n = 24) of patients and femur fracture in 3% (n = 4). In the study of Bülbül et al, femur diaphysis fracture was reported at the rate of 7.1%, which was ascribed to osteopenia developing due to immobility in paralytic lower extremities (3).

The most important causes of mortality in patients with NTD are central nervous system infection, respiratory infection, urinary sepsis and V/P shunt dysfunction. Mortality is frequently seen in newborn period and preschool period. In a retrospective study in which 383 patients were evaluated, it was reported that while mortality rate prior to discharge was 4.1%, that after discharge was 6%. Of these deaths, 39.1% occurred before the age of one (18). In the present study, the rate of mortality in early period was 5.2% and in all of these patients, defect size was 5 cm or over (Group 2).

In conclusion, NTD is a disease group with high morbidity and mortality rates in short and long term. Early surgical correction improves morbidity results in the long term and decreases complications markedly in the short term. In patients with larger defects, in spite of early surgical correction, the rate of complications is higher, duration of hospitalization and antibiotic use is longer and the rate of mortality is higher. In such patients, in order to reduce the rate of complications and mortality, it is recommended that infants with antenatal diagnosis should be delivered at centers where multidisciplinary approach is available, precautions should be taken against the problems they are likely to encounter and families should be informed beforehand on these issues.

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