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NEURODEVELOPMENTAL OUTCOMES IN PRETERM INFANTS

ERKEN DOĞMUŞ BEBEKLERDE NÖROGELİŞİMSEL SONUÇLAR

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ABSTRACT

Objective: The increasing technological equipment of neonatal intensive care units (NICU), the experienced intensive care team, and the use of supportive treatments (antenatal corticosteroid, surfactant) increased the survival rates of premature babies and therefore the morbidity rates. It was aimed at evaluating the frequency of cerebral palsy (CP) and epilepsy, which are the most common neurological problems at premature infants (≤ 34 weeks of age).

Method: Two hundred fifty-three premature infants who were born ≤ 34 weeks of age and followed between 2016 and 2020 were included in this study. Patients' gestational age, birth weight, mechanical ventilation, seizure status, internalization duration in the NICU, neurologic examinations, and Denver developmental screening test (DDST-II) of the patients were reviewed.

Result: The mean gestational age was 29.44 (24–34) weeks and the birth weight was 1225 (990–1607) grams. During the NICU stay, 26 patients (10.3%) had seizures. Seizures were the most common in 28–31-week preterms (57.7%; p=0.02). Fifty-five (21.7%) patients had abnormal DDST-II. There was a significant difference between seizures in the neonatal period and internalization duration and abnormal DDST-II (respectively p <0.001, p<0,05). Forty-six patients (15.8%) had neurodevelopmental delay, and nine (3.6%) had CP (five had hemiparetic CP, two had spastic paraplegia, and two had spastic tetraparesis). Sixteen (6.3%) patients had epilepsy; 9 (3.6%) had speech disturbance; 3 (1.2%) had hydrocephaly; 1 (0.4%) had microcephaly; and 1 (0.4%) had macrocephaly. Epilepsy was more common in patients with neonatal seizures (p<0.001).

Conclusion: Continuous developmental monitoring and evaluation allows for the early detection of developmental delays in preterm infants. Early recognition and referral to rehabilitation programs can reduce the level of sequel. We mostly encountered neurodevelopmental delay, CP, epilepsy, and speech disturbance.

Key words: cerebral palsy, DDST-II, epilepsy, preterm infants

ÖZET

Giriş: Yenidoğan yoğun bakım ünitelerinin (YYBÜ) artan teknolojik donanımı, deneyimli yoğun bakım ekibi ve destekleyici tedavilerin (antenatal kortikosteroid, sürfaktan) kullanılması, prematüre bebeklerin hayatta kalma oranlarını ve dolayısıyla morbidite oranlarını artırdı. Prematüre bebeklerde (≤ 34 hafta) en sık görülen nörolojik problem olan serebral palsi (SP) ve epilepsi sıklığının değerlendirilmesi amaçlandı.

Yöntem: Bu çalışmaya 2016-2020 yılları arasında 34 hafta ve altı doğan ve takip edilen 253 prematüre bebek dahil edildi. Hastaların gebelik yaşı, doğum kilosu, mekanik ventilasyonu, nöbet durumu, YYBÜ'de kalış süresi, nörolojik muayeneleri ve Denver gelişimsel tarama testi (DGTT- II) incelendi.

Bulgular: Ortalama gebelik yaşı 29,44 (24-34) hafta, doğum ağırlığı ise 1225 (990-1607) gramdı. YYBÜ'de kaldığı süre boyunca 26 hastada (%10,3) nöbet görüldü. Nöbetler en sık 28-31 haftalık prematürelerde görüldü (%57,7; p=0,02). Elli beş (%21,7) hastada anormal DDST-II vardı. Yenidoğan dönemindeki nöbetler ve içselleştirme süresi ile anormal DGTT- II arasında anlamlı fark vardı (sırasıyla p<0,001, p<0,05). Hastaların 46'sında (%15,8) nörogelişimsel gecikme, dokuzunda (%3,6) SP vardı (beşinde hemiparetik SP, ikisinde spastik parapleji ve ikisinde spastik tetraparezi vardı). On altı (%6,3) hastada epilepsi vardı; 9'unda (%3,6) konuşma bozukluğu vardı; 3'ünde (%1,2) hidrosefali vardı; 1'inde (%0,4) mikrosefali vardı; ve 1'inde (%0,4) makrosefali vardı. Yenidoğan nöbeti geçiren hastalarda epilepsi daha sık görüldü (p<0,001).

Sonuç: Sürekli gelişimsel izleme ve değerlendirme, erken doğmuş bebeklerde gelişimsel gecikmelerin erken tespitine olanak sağlar. Erken tanı ve rehabilitasyon programlarına yönlendirme sekel düzeyini azaltabilir. En sık nörogelişimsel gecikme, SP, epilepsi ve konuşma bozukluğuyla karşılaştık.

Anahtar Kelimeler: serebral palsi, DGTT- II, epilepsi, erken doğmuş bebekler

INTRODUCTION

In recent years, with the advancement of technology, survival rates of very low-birth-weight neonates have increased in neonatal intensive care units (NICU). However, the reduced mortality in these neonates was accompanied by increased morbidity. There are many factors affecting the neurodevelopmental prognosis of preterm infants (1).

In the early period of life, the screening studies for development and follow-up are very difficult and complicated because the problems in this period are clinically uncertain and may vary over time. Developmental screening tools include neurological examination, family surveys and interviews, the Denver Developmental Screening Test II (DDST-II), and the Bayley Scales of Infant Development-II

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(BSID-II) (2–5). Neurodevelopmental delay (NDD) is used to refer to a delay in one or more aspects of the learning and development of infants and young children. Case definitions of neurodevelopmental delays are provided by the World Health Organization (WHO). Neurodevelopmental delay was reclassified according to the International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10) criteria (6, 7).

The term neurodevelopmental delay generally does not contain precise limits. In this study, we tried to evaluate and categorize premature infants according to ICD criteria. It was aimed at evaluating the frequency of cerebral palsy (CP) and epilepsy, which are the most common neurological problems in premature infants (≤ 34 weeks of age).

MATERIALS AND METHODS

Two hundred fifty-three premature infants who were born ≤ 34 weeks of age and followed between 2016 and 2020 were included in this study. Exclusion criteria were small for gestational age, metabolic diseases, major congenital abnormalities, chromosomal abnormalities, intrauterine infection, and diabetic mothers' babies. Patients are classified according to birth weight as follows: <1000 g: extremely low birth weight (ELBW), 1000 to 1499 g; very low birth weight (VLBW), 1500 to 2500 g; low birth weight (LBW), and according to gestational age as follows: extremely preterm: <28 weeks; very preterm: 28 to 316/7 weeks; moderately preterm: 32 to 336/7 weeks (8).

Patients' gestational age, birth weight, mechanical ventilation, and seizure status were assessed. Internalization duration in the NICU, neurologic examinations, and DDST-II of the patients were reviewed. All infants were assessed with the DSST-II at the two-year age controls. The adjusted age was taken into account when determining the result of the test. If there was no delayed task or more than one warning item in the entire test, the child's development was considered normal. If the child received two or more delayed items in the entire test, his or her development

Table 1. Demographic characteristics of patients according to their gestational weeks

	Gestational Age								
	23-27 weeks		28-31 weeks		32-34 weeks		Total		*P
	n	%	n	%	n	%	n	%	
Gender									
Female	23	9.1	65	25.7	29	11.5	117	46.2	0.460
Male	22	8.7	86	34	28	11.1	136	53.8	
Birth Weight									
≤1000 gram	32	12.6	32	12.6	2	0.8	66	26.1	<0.001
1000-1500 gram	13	5.1	80	31.6	14	5.5	107	42.3	
>1500 gram	-	-	39	15.4	41	16.2	80	31.6	
Mechanical Ventilation									
Yes	21	8.3	25	9.9	5	2	51	20.2	0.024
No	24	9.5	126	49.8	52	20.6	202	79.8	
Seizure									
Yes	9	3.5	15	5.9	2	0.7	26	10.3	0.024
No	36	14.2	136	53.7	55	21.7	227	89.7	
Epilepsy									
Yes	6	2.4	9	3.6	1	0.4	16	6.3	0.560
No	39	15.4	142	56.1	56	22.1	237	3.7	
Transfontaneller USG									
Normal	29	13.1	93	42.1	41	18.6	163	73.8	0.820
Abnormal	9	4.1	37	16.7	12	5.4	58	26.2	
MRI									
Normal	1	3.8	3	11.5	-	-	4	15.3	0.810
Abnormal	5	19.2	15	57.5	2	8	22	84.7	
DDST-II									
Normal	33	13	118	46.6	48	19	199	78.7	0.400
Abnormal	12	4.7	33	13	9	3.6	54	21.3	

DDST-II: Denver Developmental Screening Test II, MRI: Magnetic resonance imaging. Significant p values are colored in bold.
* Evaluation was made based on the p value for the variables larger than a 2 x 2 contingency table for the chi-square test of independence and Fisher's exact tests.

was considered abnormal, regardless of the presence or absence of warning items. If the test contained only one delayed task, two or more warning items without delay, or one or more warning items with a delay, the child's development was considered suspicious (4). The DSST-II, which was suspicious, was considered suspicious and abnormal three months later. According to ICD-10, prepared by the WHO, developmental delay is divided into mental, behavioral, and neurodevelopmental delays. These sub-sections can be divided into: Specific Developmental Disorders of Speech and Language (SDDSL), Specific Developmental Disorder of Motor Functioning (SDDMF), Other Disorders of Psychological Development (ODPD), Unspecified Disorder of Psychological Development (UDPD), and Combination of Speech-Scholastic-motor Disorders (MSDD) (6, 7). Transfontanellar ultrasonography (TFUS) and cranial magnetic resonance imaging (MRI) were recorded.

Statistical analysis

Statistical analyses were performed using the SPSS 15.0 (SPSS for Windows, Version 15.0, Chicago, SPSS Inc.) program. Normally distributed variables were presented as the mean (standard deviation), and nonnormally distributed variables were presented as the median (minimum-maximum). In the comparison between the independent groups, the t-test was used for the parametric data and the Mann-Whitney U test was used for the non-parametric data. The difference between the categorical data was evaluated by chi-square and Fisher's exact tests. Evaluation was made based on the p value for the variables larger than a 2 x 2 contingency table for the chi-square test of independence and Fisher's exact tests. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 253 premature infants born ≤ 34 weeks of age were included in this study. Of these, 136 (53.8%) were male and 117 (46.2%) were female (male/female ratio: 1.16). The mean gestational age was 29.44 (24–34) weeks, the birth weight was 1225 (990–1607) grams, and the mother's age was 29.72 (26–33) years old. One hundred eighty-nine (74.7%) patients were single pregnancies, 57 (22.5%) patients were twins, and 7 (2.8%) patients were triple pregnancies. The demographic characteristics of the patients enrolled in the study are given in Table 1. Fifty-one (20.2%) patients needed mechanical ventilation. Forty-four (86.3%) of them needed mechanical ventilation. There was

Table 2. Demographic and clinical features of study population according to Denver II developmental screening test result

	DDST II						P
	Normal		Abnormal		Total		
	n	%	n	%	n	%	
Gender							
Female	93	36.8	24	9.5	117	46.2	0.66
Male	105	41.5	31	12.3	136	53.8	
Gestational age							
23-27 week	33	13	12	4.7	45	17.8	0.39
28-31 week	117	46.2	34	13.4	151	59.7	
32-34 week	48	19	9	3.6	57	22.5	
Mechanical Ventilation							
Yes	41	16.2	10	4	51	20.2	0.6
No	157	62.1	45	17.8	202	79.8	
Seizure in neonatal period							
Yes	13	5.1	13	5.1	26	10.3	<0.001
No	185	73.1	42	16.6	227	89.7	
Epilepsy							
Yes	10	4	6	2.4	16	6.3	0.12
No	188	74.3	49	19.4	237	93.7	
Cerebral Palsy							
Yes	-	-	9	3.6	9	3.6	<0.001
No	185	73.1	59	23.3	244	96.4	
MRI Findings							
Normal	3	11.5	1	3.8	4	15.4	0.66
Abnormal	14	53.8	8	30.8	22	8.6	

DDST-II: Denver Developmental Screening Test II, MRI: Magnetic resonance imaging.
* Evaluation was made based on the p value for the variables larger than a 2 x 2 contingency table for the chi-square test of independence and Fisher's exact tests.

Table 3. Transfontanellar USG and MRI findings of the patients

	n	%
Transfontanellar USG (n=221)		
Lateral ventricular dilatation	16	6.3
Caudothlamic cyst	10	4
Periventricular leukomalacia	9	3.6
Enlargement of frontal subarachnoid space	6	2.4
Cavum septum	4	1.6
Choroidal cyst	3	1.2
Germinal matrix hemmorhage	3	1.2
Corpus callosum dysgenesis	3	1.2
Ventricular asymmetry	1	1.2
Hemmorhage in lateral ventricul	3	0.4
Normal	163	64.4
MRI findings* (n=26)		
Periventricular leukomalacia	7	2.8
Cystic encepahlomalacia	3	1.2
Delayed myelination	2	0.8
Enlargement of frontal subarachnoid space	2	0.8
Hydrocepahly	2	0.8
Lateral ventricular enlargement	2	0.8
Thalamocaudat cyst	1	0.4
Corpus callosum dysgenesis	1	0.4
Ventricular asymmetry	1	0.4
Cavum septum	1	0.4
Intraventricular hemmorhage	1	0.4
Arnold chiari type 1	1	0.4
Normal	4	1.6

USG: Ultrasonography, MRI: Magnetic resonance imaging,
* A patient has more than one finding

a significant difference between mechanical ventilation and birth weight; the mean rank of birth weight (U = 3636, z = -3.245, p = 0.001) was lower than the ones who did not require mechanical ventilation. Preterm infants between the ages of 28 and 31 weeks were the most likely to require mechanical ventilation (25/51) (49%; p<0.001). There was a significant difference between mechanical ventilation and gestational age; the mean rank of gestational age (U = 3047, z = -4.5, p<0.001) was lower than the ones who did not require mechanical ventilation. There was a significant difference between mechanical ventilation and birth weight (p<0.001).

During the NICU stay, 26 patients (10.3%) had seizures. Eleven (42.3%) were female, while 15 (57.7%) were male. Seizures were the most common in 28–31-week preterms (57.7%; p = 0.024). Four patients (15.4%) who had seizures required mechanical ventilation. No significant relationship was found between seizure (p = 0.67), and gender (p = 0.52) for mechanical ventilation. There was a statistically significant difference between gestational age and seizure mean rank; the mean rank of gestational age (U = 2056, z = 2.56, p = 0.001) was lower than the mean rank of the ones who did not have seizures (Table 1).

Fifty-five (21.7%) patients had abnormal DDST-II. Thirty-three (60%) had one skill abnormality. 22 (40%) patients had more than one skill abnormality. Fifty-four (21.3%) patients had great motor skill abnormalities. 18 (7.1%) had a fine motor skill abnormality. 9 (3.6%) patients had abnormalities in language skills, and 5 (2%) patients had social skill abnormalities. Thirteen (23.6%) of 55 patients with abnormal DDST-II and thirteen (6.6%) of 198 patients with normal development had seizures in the neonatal period. There was a significant difference between seizures in the neonatal period and abnormal DDST-II (p <0.001). No significant relationship was found between DDST-II and gender, birth age, birth weight, mechanical ventilation, or multiparity (Table 1). There was a significant difference between internalization duration and development test abnormalities. The neonates with abnormal DDST-II had stayed in the hospital longer (U = 4322, Z = 2.35, p = 0.019) than the ones who had normal development. Two hundred and four (80.6%) patients had normal neuromotor development for their adjusted age. Forty-six patients (15.8%) had neurodevelopmental delay, and nine (3.6%) had CP (five had hemiparetic CP, two had spastic paraplegia, and two had spastic tetraparesis). Sixteen (6.3%) patients had epilepsy; nine (3.6%) had speech disturbance; three (1.2%) had hydrocephaly; one (0.4%) had microcephaly; and one (0.4%) had macrocephaly. 12 (75%) of 16 patients with epilepsy had neonatal seizures. Epilepsy was more common in patients with neonatal seizures (p<0.001). While 23.6% of those with developmental delays have neonatal seizures, 6.6% of those with normal development have seizures in newborns (p<0.001). While all patients diagnosed with epilepsy had abnormalities in the DDST-II test, 54 (22.8%) of patients without epilepsy had abnormalities in the test (p<0.001). It is more common to have epilepsy in babies born at 23–27 weeks of age compared to other premature babies. As the gestational age decreased, the probability of epilepsy did not increase significantly (p = 0.056, ŋ2 = 0.23, R2 = 0.015). There was a significant difference between abnormal development and epilepsy (p<0.001, ϒ 2=0.21, Adj. R2 = 0,28); abnormal development effects resulted in epilepsy more than those resulting in CP (p<0.001, ϒ 2=0.13, Adj. R2 = 0.28). The DDST-II test was abnormal in 59 (24.2%) of 244 individuals without CP, but only in 9 children with CP (p<0.001). While CP was not found in any of the 198 children who received a normal DDST-II test, 9.4% of the 55 children who received an abnormal DDST-II test (Table 2).

Transfontanellar ultrasonography (USG) was performed

in 221 (87.3%) patients, and 58 (22.9%) of them had abnormal USG findings. The most common findings were ventricular dilatation (6.3%), caudothalamic cyst (4%) and periventricular leukomalacia (PVL) (3.6%). Cranial MRI was performed in 26 (10.3%) patients, and 22 (84.6%) had abnormal findings. The most common MRI finding was PVL (2.8%). 18 (31.6%) of 57 patients with abnormal development had abnormal transfontanellar USG, and 39 (68.4%) of 57 patients with abnormal DDST-II tests had normal transfontanellar USG. Eight (88.9%) of 9 patients with abnormal DDST-II had abnormal MRI findings, and one (11.1%) of the 9 patients with abnormal DDST-II had a normal MRI finding. There was not any significant difference between the DDST-II and MRI findings and the transfontanellar USG (p = 0.66 and 0.28, respectively). Transfontanellar USG and MRI findings are given in Table 3.

The patient's developmental status is categorized according to ICD diagnoses. There were 44 (80%) of 55 patients with SDDMF. and there were 11 (20%) of 55 patients with MSSD due to ICD classification. 54 (21.3%) patients had a delay in great motor function skill, 18 (7.1%) had a delay in fine motor function skill, 9 (3.6%) had a delay in language skill, and 5 (2%) patients had a delay in social and personal skills. 33 (13%) patients had one skill delay, 17 (6.7%) had two skill delays, one patient had three skill delays, and four (1.6%) patients had four skill delays.

DISCUSSION

The increasing technological equipment of intensive care units, the experienced intensive care team, and the use of supportive treatments (antenatal corticosteroids, surfactants) increased the survival rates of premature babies and therefore the morbidity rates (9). The younger the gestational age of the baby, the higher the risk for complications. We used DDST-II instead of BSD-II. The implementation of the BSD-II test takes approximately 45–60 minutes and requires a trained and experienced practitioner. It provides convenience to experts in the evaluation, follow-up, correct orientation, and coordinated work of babies and young children according to their age (5). The DDST-II is a developmental screening test that assesses children from birth to 6 years of age and is more preferred because of its easier performance and shorter duration. In DDST-II, the development of the child is evaluated in four general areas: personal-social, fine motor, language, and gross motor (4, 10). When compared to children born at term, extremely preterm children have significantly lower cognitive, communicative, and motor function levels at 2.5 years (11). Unadjusted for prematurity, moderately preterm children had slower rates of cognitive, communicative, and motor development than their term-born counterparts at the age of two. Only receptive communication abilities were observed to vary once prematurity was taken into account. Also, children who are somewhat preterm exhibit greater internalizing behavioral issues (12). In this study, 59.7% of the patients were between 28-31 weeks of gestation and 26.1% had a birth weight below 1000 grams. DDST-II was abnormal in 21.3% of the patients, mostly in less than 28 gestational weeks. Fine motor skill delays were more frequently observed than speech delays. At the age of three, Göçer et al. observed that 23% of individuals who were born with birth weights of less than 1500 g and/or less than 32 gestational weeks had aberrant results on the DDST-II (13).

In this study, 75% of patients with epilepsy had neonatal seizures ($p<0.001$). Seizures occur more frequently in preterm newborns compared to full-term infants, placing them at significant risk for central nervous system damage. In preterm newborns, seizures are more likely to have a negative impact on neurodevelopment (14). Crump et al. found a strong association between preterm birth and epilepsy that increased with earlier gestational age and was not mediated by CP or other comorbidities (15). Several neurological illnesses that manifest clinically later in life are caused by abnormal brain development during prenatal life. CP, mental retardation, and behavioral abnormalities have all been linked to preterm birth and low birth weight. Low birth weight and a shorter gestational period increase the chance of developing seizure disorders such as febrile seizures and newborn seizures (16). However, research on the relationship between gestational age, birth weight, and epilepsy has not been defined. We found a significant relationship between neonatal seizures and abnormal development and epilepsy, respectively. It is more common to have epilepsy in babies born at 23–27 weeks of age compared to other premature babies, but there was no significant relationship between them.

Transfontanellar USG was performed in 87.3% of the patients, and cranial MRI was performed in 10.3% of the patients in this study. The most common findings were lateral ventricular dilatation (6.3%) and caudatelamic cyst (4%) on transfontanel USG, and periventricular leukomalacia (2.8%) and cystic encephalomalacia (1.2%) on cranial MRI. No significant relationship was detected between DDST-II and MRI findings and transfontanellar USG (respectively p=0.66, p=0.28). Several studies have reported that neonatal MRI around term can be used to predict developmental delay. In the study of Hong et al., a significant relationship was found between abnormal white matter findings on MRI and developmental delay (17). In another study using DDST II for follow-up, abnormalities in the posterior limb of the internal capsule, basal ganglia, and thalamus on diffusion-weighted MRI were associated with statistically significant poor neurodevelopmental outcome (18).

In this study, we determined that the reason we found epilepsy and developmental delay more frequently was

that we found epilepsy in CP patients more frequently. Etiologically, prematurity is responsible for 20.9% of cases of CP. Among the co-morbidities of cerebral palsy are epilepsy and intellectual disability (19). According to Jin et al., the risk of neurodevelopmental diseases (epilepsy, cerebral palsy, delayed development, mental retardation, language disorder, developmental coordination disorder, autism spectrum disorder), hearing impairment, or visual impairment increased with decreasing gestational age (20). We discovered that having CP and epilepsy was associated with an abnormal DDST-II test, but we couldn't find any link between decreasing gestational age, epilepsy, and CP.

Continuous developmental monitoring and evaluation allow for the early detection of developmental delays in preterm infants. Early recognition and referral to rehabilitation programs can reduce the level of sequelae (21). We mostly encountered neurodevelopmental delay, CP, epilepsy, and speech disturbance. Problems such as mental retardation, hearing problems, speaking problems, coordination problems, and equilibrium disorders can be seen in the advanced period (22, 23).

The study's limitations include failing to conduct the Bayley exam and failing to assess psychosocial development.

CONCLUSION

As expected, there was a significant relationship between epilepsy and CP in this study. At the same time, epilepsy developed more frequently in patients with neonatal seizures. Closer follow-up of patients with neonatal seizures seems to be important. Even if there are tests that are more in-depth than DDST II, this study is a crucial resource for DDST II in anticipating the potential risks in the centers where additional tests are not possible.

Ethics Committee Approval: This study was approved by the Bursa Yuksek Ihtisas Training And Research Hospital Clinical Research Ethics Committee and conducted in accordance with the Declaration of Helsinki (Number: 2011-KAEK-25 2010/05-16).

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

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