FT52

Geç Preterm İnfantların Düzeltilmiş Yaş 12. Ayda Nörogelişimsel Sonuçları: Prospektif Çalışma

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Amaç:
Bu çalışmada düzeltilmiş yaş 12 aylık geç preterm bebeklerin nörogelişimsel sonuçlarını değerlendirmek ve nörogelişimsel sonuçları etkileyebilecek faktörlerin araştırılması amaçlanmıştır.

Hastalar ve Yöntem:
Geç preterm ve term bebeklerin 12 aylık düzeltilmiş yaştaki nörogelişimsel sonuçları, dil, kaba motor, ince motor ve sosyal beceriler de dahil olmak üzere Ankara Gelişim Tarama Envanteri (AGTE) testi ile değerlendirildi.

Bulgular:
Çalışmada 42 erken preterm ve 58 term bebek vardı. Geç preterm ve term bebekler arasında genel gelişim, dil, kaba motor, ince motor ve sosyal etkileşim puanlarında anlamlı bir fark bulunmadı ($p > 0.05$). Kaba motor skoru geç preterm kızlarda daha düşüktü ($p < 0.05$).

Sonuç:
Bu çalışmadan belki şu çıkarılabilir: Geç preterm bebekler terme yakın olsa da yine de preterm bebeklerin bazı sorunlarını yaşarlar. Geç preterm kız bebeklerde gross motor puanının daha düşük olması böyle bir kuşkuyu akılda tutmamıza yol açmalıdır. Her ne kadar bu çalışmadaki örnek sayısı az ve böyle bir kanaate varılması için yetersiz olsa da; örnek sayısı çok daha fazla olan daha geniş ve randomize kontrollü çalışmalar yapılmasını ve bu sonuçlar alınıncaya kadar geç preterm bebeklerin nörolojik takiplerinin düzenli yapılmasını öneriyoruz. Ayrıca aynı bebeklerin daha ileri yaşlardaki nörolojik gelişmelerinin takip edilmesi ile daha ayrıntılı bilgiler elde edilebileceğini düşünüyoruz.

Anahtar kelimeler: *Geç preterm, erken nörogelişimsel sonuçlar*

Neurodevelopmental outcomes of late preterm infants at 12 months corrected age: A prospective study

Purpose:
This study aimed to evaluate the neurodevelopmental outcomes of late preterm infants at 12 months corrected age and to investigate the factors that may affect the neurodevelopmental outcomes.

Patients and Methods:
The neurodevelopmental results of late preterm and term infants at 12 months corrected age were assessed by the ADSI test including language, gross motor, fine motor, and social skills.

Results:
There were 42 late preterm and 58 term infants in the study. There were no significant differences in the general development, language, gross motor, fine motor and social interaction scores between late preterm and term infants ($p>0.05$). The gross motor score was lower in late preterm girls ($p<0.05$). Maternal hypothyroidism caused lower general and language scores in infants ($p<0.05$, $p<0.05$).

Conclusion:
The following conclusions can be obtained from this study: Although late preterm infants are close to term infants, they still experience some problems of preterm infants. The lower gross motor score in late preterm girls should lead us to keep such a suspicion in mind. Although the number of patients in this study is very few and inadequate to reach such a conclusion, we suggest that large randomized controlled trials are performed and that neurological follow-up of late preterm infants is made regularly until obtaining these results. Furthermore, we think that more detailed information can be obtained by following the same infants' neurological developments at older ages.

Key words: *late preterm, early neurodevelopmental outcomes*

Introduction:
Late preterm infants constitute approximately 75% of all preterm births. Late preterm infants are more retarded than term infants in terms of physiological and metabolic development (1). Preterm infants have a higher risk of neonatal morbidity and mortality (2). Although it has been reported in the literature that late preterm infants have neurological problems, learning difficulties, low school success, and behavior problems, their prevalence rates are not exactly known (3). However, there are few studies evaluating the neurodevelopmental outcomes of late preterm infants (3). The number of studies on this subject in Turkey is very few.
Some tests are used to evaluate the neurodevelopmental outcomes of infants and children, to determine their prognosis and to start treatment early. One of these tests is the Ankara Developmental Screening Inventory (ADSI). It is a screening inventory which has been developed to determine the development and skills of infants and pre-school children, has been organized according to various age groups, and has been internationally validated (4).
In this study, we aimed to compare the neurodevelopmental outcomes of late preterm and term infants at 12 months corrected age and to investigate the factors that may affect the neurodevelopmental outcomes.

Method
The ADSI was conducted on 42 late preterm and 58 term infants of twelve mounths, corrected age, who were referred to the XXXXXX/XXXXXXX to determine their neurological developmental status. The ADSI is beneficial in the early detection of infants and children suspected of carrying a risk of developmental retardation and disorders. ADSI is a scale extensively used in Turkey for the evaluation of language–cognitive, fine motor, gross motor, social interaction skill and self-care ability levels of children between 0 and 6 years of age. Complete or partial improvements in the neurological findings are evaluated according to ADSI and the findings on the neurological examinations (8).
Multiple pregnancies were also included in the present cross-sectional study. Exclusion criteria were major anomalies, prenatal infection history, and teratogenic drug and alcohol exposure during the intrauterine period of the fetus. The present study was initiated subsequent to the permission from the XXXX Ethics Committee of XXXXXX. Consent forms were obtained after the participating families were completely informed about the aims of the present study. Necessary information about the participants as well as their medical records were written on the registration form.

Statistical Analysis
The SPSS package program 20.0 was used to analyze the data obtained. The categorical variables were presented as the frequency and percentage rate, and the numerical data were presented in the form of numerical variables as mean ± sd. The Kolmogorov–Smirnov and

Shapiro–Wilk tests were performed on the rational variables to determine their normal distribution. Student's *t*-test was used for the group comparison of variables with a normal distribution between two groups and ANOVA for multiple groups. The Mann–Whitney*U*test was employed for two independent groups as a non-parametric method and the Kruskal–Wallis test for multiple groups. Binary comparisons were made during multiple group comparisons. To determine the relations among the categorical variables, thechi-square test with a Monte Carlo simulation was applied. In the study, the type I error level was determined as 5%, and the outcomes were considered statistically significant when the probability was $p < 0.05$.

Results

100 patients were included in the study (42 late preterm, 58 term). When the demographic characteristics of the patients were examined, multiple pregnancy ($p<0.05$), cesarean section ($p<0.05$) and assisted reproductive technique ($p<0.05$) were found significantly higher in late preterm infants compared to term infants. Birth weight was found significantly higher in term infants compared to late preterm infants ($p<0.05$) There was no significant difference between the two groups in terms of maternal age and gender ($p>.05$, $p>0.05$) (Table 1).

Maternal preeclampsia/eclampsia and amniotic fluid volume changes were higher in late preterm infants compared to term infants ($p<0.05$) (Table 1).

The mean ADSI scores of late preterm and term infants are shown in Table 2. There were no significant differences in the general development, language, gross motor, fine motor and social interaction scores between late preterm and term infants ($p>0.05$).

The mean ADSI scores of late preterm and term infants were compared according to their demographic characteristics (Table 3). When late preterm infants were compared in terms of gender, the gross motor score was lower in late preterm girls ($p<0.05$).

The effects of maternal and neonatal factors on the neurodevelopmental outcomes are shown in Table 4. The presence of maternal hypothyroidism had a significant effect on the general and language scores. The infants of the mothers with a history of hypothyroidism had lower general and language scores ($p<0.05$, $p<0.05$).

Discussion

This is the first study to evaluate the early neurodevelopmental results in late preterm and term infants by the ADSI test. Prenatal, natal and postnatal factors may cause poor neurological outcomes in preterm infants (6). Moreover, brain development occurs especially in the last six weeks of pregnancy (7). Preterm birth affects brain development and neurobiological processes (8).

Late preterm infants have been shown to have twice the risk of neurodevelopmental disability compared to term infants. The spectrum of neurodevelopmental disabilities such as sensory and cognitive impairment, attention deficit, hyperactivity, emotional symptoms, communication, and learning difficulties are quite extensive in preterm infants (3). It was reported that neurodevelopmental impairment was most commonly found in cognitive (9) and motor (10) functions in late preterm infants and that the mean cognitive and language scores were lower in late preterm infants than in term infants (9). Similarly, cognitive deficits were also reported in school-age children born late preterm (11). In one study, it was found that there was a 24% difference in learning scores between late preterm and term infants in the first period of education (12). In our study, there was no significant difference between late preterm and term infants in terms of general development, language-cognitive, gross motor, fine motor and social development in the early period.

There are studies in the literature showing that gender has different effects on the neurodevelopmental outcomes. In one study, male gender was reported to be more risky in

terms of cognitive functions (9). Similarly, Cserjesi R et al. (11) showed that late preterm boys caught up to their peers, whereas late preterm girls lagged behind their peers during the school-age years. Romeo et al. (13) reported that the mental developmental index was lower in late preterm boys at 12 and 18 months uncorrected age, but it showed similar results between the genders when corrected age was used. In our study, there was no significant difference between the genders in terms of cognitive functions. Cognitive scores were not found to be low in some studies where corrected age was used (13,14,15). These studies support our results. In addition, we observed that the ADSI-gross motor functions of late preterm boys were better than those of late preterm girls. The difference in the social development score was not significant, but it was slightly higher in late preterm girls.

There are few studies investigating the predictors of adverse outcomes of late preterm infants. In studies conducted, it was found that preeclampsia was associated with long-term cognitive (16,17) and behavioral (18) sequelaes. In our study, preeclampsia was not found as a risk factor for neurodevelopmental disorders.

The association between raised maternal TSH levels and neurodevelopmental compromise is not clear. Williams F et al. (19) found that the general cognitive index and verbal and perceptual performance subscale scores were significantly lower in infants who were born before 34 weeks of pregnancy and had higher maternal TSH levels at birth. It has been shown that untreated maternal hypothyroidism in pregnancy is associated with poor neurophysiological outcome (20). In our study, we observed that the ADSI-general and language scores were lower in infants having maternal hypothyroidism.

The underlying mechanisms of the relationship between breastfeeding and neurological development are uncertain. Infants who received breast milk in the neonatal intensive care unit had less autism symptoms (21). Johnson S et al. (9) have indicated that early cessation of breastfeeding at hospital discharge is associated with moderate/severe cognitive deficits in infants. In our study, we found that the general and language scores were higher in late preterm infants who received breast milk for longer than 6 months.

Conclusion, prematurity continues to be one of the major causes of infant mortality and life-long morbidity. Although late preterm infants are close to term infants, they still experience some problems of preterm infants. The lower gross motor score in late preterm girls should lead us to keep such a suspicion in mind. Although the number of patients in this study is very few and inadequate to reach such a conclusion, we suggest that large randomized controlled trials are performed and that neurological follow-up of late preterm infants is made regularly until obtaining these results. Furthermore, we think that more detailed information can be obtained by following the same infants' neurological developments at older ages.

Author contribution

H.A., N.T. and N.K.. designed the study; N.K. performed experiments; H.A.,N.T. and N.K.collected and analysed data, wrote the manuscript; N.T and N.K. All authors read and approved the final manuscript.

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Table 1. Characteristics of study population, n (%)

	Late Preterm n(%)	Term n(%)	*p*
Maternal & Neonatal characteristics			
Maternal Age (<35 age)	36(85,7)	43 (74,2)	*0,230*
Multiple Pregnancy	7 (16,7)	2 (3.4)	*0,023*
C/S	40 (95,2)	36 (62.1)	*<0,001*
Assisted Reproductive Techniques (yes)	3(7,1)	0(0)	*0,04*
Male	21 (50)	29 (50)	*1,000*
Birth Weight (gr)	2,55±0.49	3,20±0,44	*<0,001*
Neonatal Morbidity Factors			
Congenital pneumonia	2 (4,8)	0 (0)	*0,095*
Pulmonary cystic malformation	1 (2,4)	0 (0)	*0,240*
Respiratory distress syndrome	2 (4,8)	0 (0)	*0,095*
Early neonatal sepsis	3 (7,1)	0 (0)	*0,040*
Jaundice	32 (76,2)	29 (50)	*0,008*
Phototherapy	16 (38,1)	11 (19)	*0,034*
NICU hospitalization period (day)	3,64±5,28	0,79±2,49	*<0,001*
Maternal morbidity			
Diabetes mellitus	6 (14,3)	3 (5,2)	*0,118*
Preeclampsia/eclampsia	11 (26,2)	0 (0)	*<0,001*
An/poly/oligohydramnios	6 (14,3)	1 (1,7)	*0,016*
Hypothyroidism	4 (9,5)	5 (8,6)	*0,877*
Early membrane rupture	2 (4,8)	2 (3,4)	*0,742*
Urinary Tract Infection	21 (50)	19 (32,8)	*0,084*

Table 2. ADSI Scores of Late Preterm and Term Babies

ADSI Subtests	Late Preterm n=42	Term n=58	
	Mean±ss	Mean±ss	*p*
ADSI General	73,90±10,45	73,51±10,56	*0,856*
ADSI Language	23,33±3,96	23,12±3,87	*0,789*
ADSI Fine motor	14,52±1,25	14,48±1,50	*0,885*
ADSI Gross motor	15,29±3,32	15,03±3,57	*0,722*
ADSI Socialization	21,12±2,73	21,02±3,25	*0,869*

Table 3. Comparison of ADSI Scores and Demographic Characteristics of Late Preterm and Term Babies

								ADSI
	General			Language			Fine motor	
	Late preterm	Term	*p*	Late preterm	Term	*p*	Late preterm	Term
Delivery								
CS	74,1±10,7	74,1±7,8		23,4±3,9	23,3±3,3		14,5±1,3	14,4±1,3
Vaginal birth	71,0±4,2	72,5±14,6		22,5±4,9	22,8±4,4		14,5±0,7	14,5±1,9
p	*0,595*	*0,962*		*0,753*	*0,910*		*1,000*	*0,491*
Gender								
Female	73,04±8,45	74,06±10,2		23,2±3,6	23,4±3,5		14,71±1,1	14,7±1,4
Male	74,16±12,3	72,96±11,1		23,5±4,4	22,9±4,2		14,33±1,4	14,3±1,6
p	*0,588*	*0,889*		*0,920*	*0,833*		*0,293*	*0,550*
Jaundice(n)	74,2±10,8	73,9±8,2	*0,718*	23,7±3,9	23,4±3,4	*0,761*	14,5±1,3	14,4±1,2
Breastfeeding								
no	70± …	72,83±6,3		22± …	22,8±2,2		13± …	14,3±1,0
1-6 month	73,67±13,51	73,6±10,9		23,33±5,13	23,2±4,0		14,4±1,2	14,5±1,6
6-12 month	74,19±8,74	73,5±10,6		23,4±3,3	23,1±3,9		14,7±1,3	14,5±1,5
p	*0,924*	*0,869*		*0,946*	*0,850*		*0,396*	*0,799*