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NEÜ YAYINEVİ

Neurodevelopmental Outcomes of Moderate/Late Preterm Infants At 11-12 Years of Age

Orta/Geç Preterm Bebeklerin 11-12 Yaş Arası Nörogelişimsel Prognozu

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Öz

Amaç: Orta/geç preterm doğan 11-12 yaşındaki çocukların nörogelişimsel sonuçlarını ve okul başarısını araştırmayı ve prognozu etkileyen risk faktörlerini belirlemeyi amaçladık.
Hastalar ve Yöntem: Yenidoğan yoğun bakım ünitesinde Ocak 2004-Aralık 2004 tarihleri arasında izlenen orta ila geç preterm bebekler çalışmaya dahil edildi; çocuklar 2016 yılında hastanemiz pediatri polikliniğinde muayene edildi. Perinatal ve neonatal dönem öyküleri hastane veri tabanından elde edildi. Somatik büyüme özellikleri yorumlandı. Nörogelişim, Wechsler Çocuklar İçin Zeka Ölçeği (WISC-R) ölçeği kullanılarak değerlendirildi. Pediatrik Semptom Kontrol Listesi (PSC) uygulandı. Sosyoekonomik düzeyin nörogelişimsel sonuç üzerindeki etkisi incelendi. Okul performansı karne notları kullanılarak değerlendirildi.
Bulgular: Yaş ortalaması 11.6 olan 41 çocuk değerlendirildi. Somatik büyüme ile ilişkili risk faktörleri anne yaşı (>35 yaş), fetal distres ve patent duktus arteriyozus idi. Sepsis, sözel zekada bir azalma ile ilişkilendirildi; periventriküler lökomalazi hem sözel hem de performans zekası üzerinde olumsuz etkilere sahipti. Sosyoekonomik düzey, performans ve tam ölçekli zeka ile orta düzeyde bir korelasyon gösterdi. PSC puanı pozitif olan çocukların zeka bölümü anlamlı olarak daha düşüktü.
Sonuç: Orta ila geç preterm bebekler, beynin tam olgunlaşmaması ve doğum sorunları nedeniyle hem nörolojik hem de gelişimsel olarak geride kalmaktadır. Erken prematüre bebeklere benzer şekilde, bu çocuklar uzun süre izlenmelidir; aile desteği, rehabilitasyon ve özel eğitim ihtiyaçları karşılanmalıdır.

Anahtar Kelimeler: Ergen sağlığı, okul performansı, zeka, nörolojik prognoz

Abstract

Aim: We aimed to investigate the neurodevelopmental outcomes and school success of 11- to 12-year-old children born as moderate/late preterm infants and identify risk factors affecting prognosis.
Patients and Methods: Moderate/late preterm infants followed in the neonatal intensive care unit between January 2004 and December 2004 were included, and the children were examined again in our pediatrics outpatient clinic in 2016. Perinatal and neonatal histories were obtained from the hospital database. Physical growth characteristics were interpreted. Neurodevelopment was evaluated using the revised Wechsler Intelligence Scale for Children (WISC-R). The Pediatric Symptom Checklist (PSC) was also applied. The effect of socioeconomic level on neurodevelopmental outcome was examined. School performance was evaluated using report card grades.
Results: Forty-one children with a mean age of 11.6 years were evaluated. Risk factors associated with physical growth outcomes were maternal age of >35 years, fetal distress, and patent ductus arteriosus. Sepsis was associated with a decrease in verbal intelligence while periventricular leukomalacia had negative effects on both verbal and performance intelligence. Socioeconomic level showed a medium correlation with performance and full-scale intelligence. The intelligence quotients of the children with positive PSC scores were significantly lower.
Conclusion: Moderate/late preterm infants lag both neurologically and developmentally due to incomplete maturation of the brain and natal problems. Similar to early preterm infants, these children should be monitored for extended periods, and family support, rehabilitation, and special education needs should be met.

Keywords: Adolescent health, school performance, intelligence, neurological prognosis

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INTRODUCTION

In recent years, prematurity has increased by 25% around the world, and moderate/late preterm infants constitute a significant proportion of this group (1). In 2021, the preterm birth rate in the United States was reported as 10.49% and the late preterm birth rate was 7.67%, the highest rate in recent years (2). Some studies have shown that preterm infants have higher rates of motor deficits, cognitive dysfunction, and behavioral problems than those born at full term (3,4).

Neurodevelopmental and behavioral problems detected in moderate/late preterm infants are largely attributed to incomplete brain maturation, as the brain development at 34 weeks is reported to be approximately 65% of that of the full-term brain (5). Although many studies have explored the neurodevelopment of early preterm infants, studies on the long-term follow-up and etiological risk factors of late premature infants are limited, especially at school age.

The present study was therefore undertaken to examine the neurological and developmental outcomes of moderate/late preterm infants and to investigate the factors affecting school performance and neurodevelopment.

PATIENTS AND METHODS

Patient Group

Moderate/late preterm infants who were followed in the Bakırköy Maternity and Pediatrics Hospital Neonatal Intensive Care Unit between January 2004 and December 2004 were included in the study. Those who were born between 32 weeks + 0 days and 33 weeks + 6 days of gestation were moderately preterm, while those born between 34 weeks + 0 days and 36 weeks + 6 days were late preterm. Term infants and infants with congenital malformations, genetic syndromes, or metabolic diseases were excluded. Demographic characteristics and perinatal and neonatal information were obtained from patient files, and follow-up information was obtained from outpatient clinic cards. The families were called via phone and appointments were scheduled with the participants of the research. Families and children were informed about the purpose of the study and informed consent was obtained.

Assessment of Risk Factors

Advanced maternal age, premature rupture of membranes (PROM), chorioamnionitis, placental dysfunction, chronic disease, hypertension, and smoking or substance use were investigated as perinatal risk factors. As neonatal risk factors, gestational week, Ballard score, and intrauterine growth were investigated, and data were also collected about morbidities in the neonatal period, including low Apgar score, respiratory distress syndrome (RDS), need for mechanical ventilation, bronchopulmonary dysplasia, intracerebral hemorrhage (ICH), hydrocephalus, necrotizing enterocolitis, retinopathy of prematurity (ROP), sepsis/meningitis, patent ductus arteriosus (PDA), hypoglycemia, and hyperbilirubinemia. Infants' diets were recorded as having been composed of breast milk and/or formula and mothers were asked about the duration of breastfeeding.

Examinations and Tests

The children were examined in our pediatrics outpatient clinic in 2016. Parents were asked during interviews about the children's health problems and growth characteristics. Information was also collected about the children's preschool education and special education needs. In the evaluation of school performance, grades from Turkish language courses were used for verbal scores and grades from mathematics courses were used for performance scores. Behavioral problems were recorded using the Pediatric Symptom Checklist (PSC) (6). The socioeconomic characteristics of the families were evaluated with a questionnaire form consisting of 13 questions that addressed the parents' monthly income, education, and occupation and the home environment. In total, scores from this questionnaire below 26 points were determined to reflect low, scores of 26-39 medium, and scores above 39 high socioeconomic levels.

Detailed physical and neurological examinations were performed. Height and weight values were situated on percentile curves for Turkish children (7). Cerebral palsy, intellectual disabilities, blindness, and posthemorrhagic hydrocephalus were considered major neurological deficits, whereas minor deficits included disorders of balance, muscle tone changes, speech disturbances, refractive errors, strabismus, and mild hearing deficits. Following these examinations, participants were directed to the psychologist for administration of the revised Wechsler Intelligence Scale for Children (WISC-R) (8).

Statistical Analysis

IBM SPSS Statistics 20 (2011) was used for statistical analysis. Data were analyzed using the chi-square test, Fisher exact test, McNemar test, and independent-samples t-test. Pearson correlation

analysis was used to compare two continuous variables. For statistical significance, $p<0.05$ was accepted at the 95% confidence interval. The ethics committee of our hospital (10.03.2015/15932) approved the study.

RESULTS

A total of 41 children (18 girls and 23 boys) with a mean age of 11.6 years (140.8 months) were evaluated. Thirty-three (80.5%) of these participants were born as preterm infants appropriate for gestational age, while 8 (19.5%) were born as infants with intrauterine growth restriction (IUGR). The mean gestational age was 34.3±1.2 weeks and the mean birth weight was 1780±310 g. When perinatal risk factors were examined, it was seen that 9.8% of mothers had hypertension during pregnancy, 4.9% had gestational diabetes, and 2.4% had PROM; fetal distress was present in 7.3% of the cases. Perinatal and neonatal risk factors are summarized in Table 1.

Table 1. Perinatal and Neonatal Risk Factors of the Cases

Perinatal Risk Factors		
	n	**%**
Maternal age >35 y	39	95.1
IUGR	8	19.5
Hypertension	4	9.8
Fetal distress	3	7.3
Gestational Diabetes	2	4.9
PROM	1	2.4
Placental abruption	0	0.0
Neonatal Risk Factors		
	n	**%**
TTN	20	48.8
Hyperbilirubinemia	18	43.9
Hypoglycemia	7	17.1
Sepsis	6	14.6
ICH	4	9.8
ROP	4	9.8
Hydrocephalus	3	7.3
PVL	3	7.3
Mechanical ventilation	2	4.9
PDA	2	4.9
Apnea	2	4.9
RDS	1	2.4
Meningitis	1	2.4
NEC	1	2.4
Congenital Heart Defect	1	2.4

*Independent risk factors
**IUGR: intrauterine growth restriction , PROM: premature rupture of membranes, TTN: transient tachypnea of the newborn, ICH: intracerebral hemorrhage, ROP: retinopathy of prematurity, PVL: periventricular leukomalacia, PDA: patent ductus arteriosus, RDS: respiratory distress syndrome, NEC: necrotising enterocolitis

ROP was detected in 4 infants (9.8%), and 2 of those cases were classified as Stage 2 and while 2 cases were Stage 3. Four preterm infants (9.8%) had ICH, and 3 of those cases were Stage 1 while 1 case was Stage 3. Regarding nutrition, 6 patients (14.6%) were never breastfed; the average duration of breastfeeding was 10.9 months (range: 1-36 months).

The neurological examinations of 37 children (90%) were within the normal limits. Intellectual disabilities (IQ of <70) in 3 cases and unilateral blindness in 1 case were defined as major neurological sequelae. Among the 3 patients with minor neurological deficits, 2 (5%) were followed for strabismus and 1 patient had gait disturbance (Table 2). Three children (7%) had learning disabilities, 4 (10%) had special educational needs, and 4 (10%) had a diagnosis of autism spectrum disorder (ASD). According to the PSC results, the scores of 4 children were above the threshold of 28, and they were evaluated by a child psychiatrist. The WISC-R scores of children with higher PSC scores were found to be significantly lower ($p<0.001$).

Considering the relationship between perinatal risk factors and WISC-R scores, advanced maternal age (>35 years), hypertension, gestational diabetes, fetal distress, and low Apgar score did not have significant effects on WISC-R scores ($p>0.05$). There was also no significant effect of gestational week or breastfeeding duration on WISC-R scores ($p>0.05$). Of the morbidities in the neonatal period, it was observed that the mean verbal intelligence score of the patients with sepsis was significantly lower ($p=0.019$), while the differences in their performance and full-scale intelligence scores were insignificant ($p=0.788$ and $p=0.197$, respectively). It was found

Table 2. Abnormal Neurological and Behavioral Findings of the Cases

Neurological Findings	**n**	**%**
Intellectual disability	3	7.3
Visual Problems		
Strabismus	2	5
Blindness	1	2.5
Hearing/speech impairment	0	0
Cerebral palsy	0	0
Gait-balance disorder	1	2.5
Behavioral Disturbances	**n**	**%**
PSC positive	4	10
Learning difficulty	3	7.3
Special education	4	10
Autism spectrum disorder	4	10

Table 3. Verbal and Performance Intelligence Scores According to Maternal, Perinatal and Neonatal Risk Factors

Risk Factors	Verbal Intelligence Score Mean ± standard deviation	p[a]	Performance Intelligence Score Mean ± standard deviation	p[a]
Maternal age> 35 yrs	80±4.2	0.329	86.5±7.8	0.499
IUGR	94.8±23.3	0.800	97.1±20.2	0.733
Gestational diabetes	96.5±4.9	0.806	91.5±14.8	0.777
Maternal hypertension	87.8±13.4	0.562	95.8±7.9	0.943
Fetal distress	88.7±15.3	0.680	92.3±11.5	0.787
ROP	77±20.6	0.078	84.8±6.7	0.235
Hydrocephalus	100±6.6	0.532	101±10.8	0.568
Hypoglycemia	90.3±12.8	0.670	98.6±6.2	0.320
Sepsis	84.5±5.5	**0.019**	97±7	0.788
Mechanical ventilation	104.5±16.3	0.402	98±8.5	0.822
ICH	87.8±22	0.562	89.3±11.8	0.504
PDA	101.5±23.3	0.539	116±11.3	0.097
Apnea	105±15.6	0.382	97.5±9.2	0.852
Hyperbilirubinemia	91.3±23.8	0.597	93.2±21.5	0.549
PVL	58.7±19.6	**0.001**	73±30	**0.027**
TTN	89.3±21.2	0.215	93.5±21.8	0.584

[a]**Independent T test**

IUGR: intrauterine growth restriction, ROP: retinopathy of prematurity, ICH: intracerebral hemorrhage, PDA: patent ductus arteriosus, PVL: periventricular leukomalacia, TTN: transient tachypnea of the newborn

that children with periventricular leukomalacia (PVL) had low scores in all areas (p=0.001, p=0.027, and p=0.002, respectively) (Table 3).

The report card grades for Turkish and mathematics were significantly higher among girls than boys (p=0.041 and p=0.037, respectively). On the other hand, no statistically significant difference was found between the full-scale intelligence scores of the genders (p=0.127). Five children (12%) had families with a low socioeconomic level, 32 (78%) had families with a medium socioeconomic level, and 4 (10%) had families with a high socioeconomic level. The high school or university graduation rates of the mothers and fathers were 37% and 51%, respectively; the income level was at the minimum wage in 20% of families and the rate of consanguineous marriage was found to be 15%. Thirty-two percent of the children did not have preschool education. Moderate correlations were found between performance and full-scale intelligence scores and socioeconomic level (p=0.007 and p=0.009, respectively), while no significant relationship was found with verbal intelligence score (p=0.052).

According to the WISC-R results, 1 child (2.5%) had moderate intellectual disability and 2 (5%) had mild intellectual disability. Three (7%) had borderline intelligence, 8 (20%) had low-average IQs, and 21 (51%) had average intelligence. Five (12%) had high-average IQs, and 1 child (2.5%) had very superior intelligence. There was a strong positive correlation of verbal intelligence with Turkish grades and a moderate positive correlation with mathematics grades. There was a moderate correlation of performance scores with Turkish and mathematics grades. On the other hand, a strong relationship was found between full-scale intelligence scores and both Turkish and mathematics grades. Verbal (p<0.001), performance (p=0.002), and full-scale intelligence scores (p<0.001) were found to be significantly lower among children with higher PSC scores.

We observed that 5 of the children (12.2%) were below the 10th percentile for height and 10 (24.4%) for weight. Weight and height percentile values at birth were compared with the current measurements and the change in height growth was found to be significant, while the change in weight values was insignificant (p=0.021 and p=0.189, respectively). Maternal age of >35 years, fetal distress, and PDA were found to be significant perinatal and neonatal risk factors of the children below the 10th percentile for current height (p=0.012, p=0.035, and p=0.012, respectively). No significant relationship was found between current weight and risk factors. There were also no significant relationships between birth height, birth weight, current height, or current weight and IQ.

DISCUSSION

It is suggested in the literature that moderate/late preterm infants are at risk of neurocognitive difficulties and behavioral and attention problems

in childhood, which may result in declines in academic performance and relationships with peers (9,10). Chan et al. reported that at age 7, children born as late preterm infants had poorer academic performance compared to their full-term peers, with a 36% higher risk of achievement below the expected academic level (11). In a recent study performed in Stanford, California, 72,316 students from an urban school district were evaluated for school performance according to their gestational ages and it was reported that moderate/late preterm births were associated with a significantly increased risk of poor academic performance, chronic absenteeism, and suspension (12). In this study, we aimed to examine how certain risk factors experienced by moderate/late preterm infants from the perinatal period up to the age of 11-12 years affected the neurodevelopment, behaviors, and school performance of the children.

When school performance was evaluated in relation to gender, Turkish and mathematics grades were higher among girls than boys, but there was no gender difference between cases with and without cognitive deficits. The cognitive functions of boys born as early preterm infants were previously reported to be delayed in comparison to girls at 6 years of age (13). Looking at anthropometric measurements, 5 (12.2%) of the children were below the 10th percentile for height and 10 (24.4%) for weight. In relation to perinatal risk factors, while advanced maternal age of >35 years, fetal distress, and PDA were significant for height (p=0.012, p=0.035, and p=0.012, respectively), no significant relationship was found between weight and risk factors. Heinonen at al. (14) examined the neurocognitive outcomes of 786 adults born as full term or late preterm infants and reported that late preterm birth may not increase the risk of poorer neurocognitive functioning in adulthood. However, the double burden of being born late preterm and being small for gestational age (SGA) did increase that risk. Another previous study concluded that SGA status may be an additional risk factor for cognitive problems in adulthood among those born late preterm (15). In our study, no relationship was found between IQ scores and gestational week and/or IUGR. This may be due to the small size of our patient group.

It was previously emphasized that there is a significant increase in neurodevelopmental delay in infants with a complicated neonatal course and that late preterm infants without morbidities in the neonatal course exhibit the same neurological performance as term infants (16). In a recent study, neonatal hypoglycemia was found to be an independent factor associated with significant neurodevelopmental impairment (17). We observed that verbal intelligence was significantly lower in premature infants who had a history of sepsis (p=0.019). Akar et al. (18) reported that sepsis is a risk factor for neurodevelopmental delay in both moderate/late and early preterm cases. Van der Ree et al. (19) evaluated the motor, cognitive, and behavioral outcomes of school-aged children with histories of early preterm birth and late-onset sepsis and reported that preterm children with late-onset sepsis tended to have more motor problems, lower IQs, and impaired memory and attention compared to controls matched for gestational age.

ICH is a morbidity that causes cognitive, sensory, and behavioral problems. It was reported that children with ICH experienced more neurodevelopmental problems, and the rate of sequelae was higher in those with stage III-IV hemorrhage and those with PVL (20). In our study, ICH was identified in 4 patients. We found no significant difference in the IQs of these patients, which may be related to the small number of cases in the present study. On the other hand, verbal, performance, and full-scale intelligence scores of patients with PVL were found to be significantly lower, consistent with the findings in the literature (21).

In our study, major neurological sequelae were identified in 4 children (10%), 3 patients had intellectual disabilities (IQ of <70), and 1 patient had unilateral blindness because of retinal detachment. Interestingly, that case of blindness was seen without a history of ROP. Our patients with cognitive problems were preterm infants with families of middle or low socioeconomic status and with morbidities such as low birth weight, ICH, PVL, and autism. All of them were receiving special education. None of our patients had a diagnosis of cerebral palsy. Martínez-Nadal et al. (10) emphasized the influence of social factors such as maternal education and socioeconomic status on the processes of catching up in late preterm populations. It was also stated in the literature that lower gestational age in association with low socioeconomic status had a synergic effect, worsening the neurodevelopmental outcomes of late preterm infants (22). In our study, a moderate positive correlation was found between socioeconomic status and both performance and full-scale intelligence scores, and no significant correlation was found with verbal intelligence scores.

Three children (7%) in our study group had learning disabilities, 4 (10%) had special educational

needs, and 4 (10%) had a diagnosis of ASD. The risk of ASD for late preterm infants was reported to be 2 to 4 times greater than that for term infants (23). In a study from Sweden, 4,061,795 infants born in 1973-2013 were evaluated for ASD and ASD prevalences by gestational age at birth were found to be 6.1% for extremely preterm, 2.6% for very to moderately preterm, 1.9% for late preterm, 2.1% for all preterm, 1.6% for early term, and 1.4% for term infants (24).

It was previously reported that late preterm infants whose behavioral problems became evident from school age were 1.68 times more likely to show attention deficits, 2.04 times more likely to show aggressive disorders, and 3.59 times more likely to show introversive personalities compared to their term peers. In the same study, a significantly higher frequency of attention deficits, aggressiveness, and withdrawal was reported in late preterm children compared to their term peers and a significant difference was found in PSC scores (25). In our study, IQ scores were found to be significantly lower in patients with higher PSC scores. This is an important finding in terms of raising awareness among physicians of the possibility of such outcomes regardless of the education and income levels of the families.

Our study may be criticized for having a limited number of cases. As another limitation, the patient files used were old and in written paper form; therefore, it could be argued that there was a slight decrease in reliability. Furthermore, the factors that could be effective in the analyses were not controlled by statistical methods. Studies involving large multicenter case series should be conducted in the future.

In conclusion, the neurodevelopment of moderate/late preterm infants is adversely affected due to incomplete brain development, morbidities in the neonatal period, and nutrition and growth problems. On the other hand, because of low socioeconomic levels and inadequate parental education, lack of multidisciplinary follow-up, and lack of preschool education and rehabilitation support, these children may experience serious neurological and psychological problems both in and out of school. Parental education is important for the detection and management of problems in neurodevelopment. The multidisciplinary follow-up of these children in neurology, ophthalmology, psychiatry, psychology, and physical therapy clinics is of crucial importance, and the detection of developmental delays and early intervention by providing education for parents can improve problems such as school failure, behavioral disorders, depression, aggression, and schizophrenia, which may be seen in late childhood and adolescence.

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