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Neurodevelopmental and psychiatric assessments at corrected age of 1-3 years in very preterm infants

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Summary

Aim: To assess the neurodevelopmental and psychiatric outcomes of very preterm vs preterm infants at 1-3 years of corrected age.

Material and Method: Between the years of 2005 and 2008, premature infants followed-up in the NICU designated as Group 1 (<32 wks;n=36) were evaluated in comparison to Group 2 (33-37wks; n=56) with the approval of Ethics Committee (TUTFEK 2008/083) in terms of neurodevelopmental and psychiatric development by using the Denver Developmental Screening Test and The Brief Infant Toddler Social Emotional Assessment-Childcare Provider Version. Mothers' psychiatric symptoms were assessed by The Brief Symptom Inventory. The socioeconomic status was determined by using SES scale; t-test or Mann-Whitney U tests, chi-square and Spearman tests were used for statistical analysis.

Results: In Group 1, paternal education level and psychodevelopmental score was lower than Group 2 and an abnormal outcome in the Denver Developmental Test was observed more frequently. The psychiatric problem score was higher in boys, whereas the psychodevelopmental score was higher in girls. The psychosocial developmental score was lower in those infants with IVH and this score showed positive correlation with the Denver Developmental Test results. There was no difference between the two groups in terms of the Brief Symptom Inventory.

Conclusions: Although very preterm infants more frequently showed abnormal neuropsychological development, they were not significantly different with regard to psychiatric problems. Girls were more advantegous than boys in terms of psychodevelopment. We conclude that these findings should be validated by larger and further studies. *(Turk Arch Ped 2011; 46: 271-6)*

Key words: Preterm infant, very preterm infant, neurodevelopment, psychiatric assessment

Introduction

The positive advances in medical technology in recent years have caused to an increase in survival rates of preterm infants, while bringing concerns about the functionality and prognosis of these infants forward. Preterm newborns are exposed to medical complications including severe respiratory problems, intraventricular bleeding (IVB) and hydrocephaly with a higher rate and thus may carry damages which can have negative effect on the central nerveous system in the long term. It has been reported that children of families with a low socioeconomic level are born prematurely and these children have a high risk in terms of experiencing behavioral and emotional problems. Cognitive, motor and behavioral problems frequently occur in children who are born prematurely and these problems frequently lead to school problems in the future. It is known that especially children born before the 32nd gestational age who are defined as the high risk group and as very preterm infants carry an increased risk in terms of development (1-4). When children who were born as very small for gestational age were compared to children who were born as appropriate for gestational age, these children were found to experience behavioral problems and problems in relation with peers with a higher rate and their level of hyperactivity was found to be higher (5). In studies performed in school-age children who were born as small for gestational age (<2500 g) and as very small for gestational age (<1500 g), findings related to cognitive, educational and behavioral disorders were obtained in these children (6-9).

In line with these data, our study aimed to compare the results of neurodevelopmental and psychiatric evaluation of very preterm infants (born before the 32nd gestational age and/or with a birth weight of less than 1500 g) and moderate-borderline preterm infants (born at the 33-37th gestational age and/or with a birth weight of more than 1500 g) followed up in Trakya University Medical Faculty Neonatalogy Unit at the corrected age of 1-3 years.

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Material and Method

The study group (group 1) included pretem infants who were born before the 32nd gestational age or with a birth weight of less than 1500 g followed up in Trakya University Medical Faculty, Department of Pediatrics, Neonatalogy Unit between the dates of 06.01.2005 and 06.30.2008, discharged from the unit and reached to the adjusted age of 1-3 years. The control group (group 2) included preterm infants who were born between the 33-37th gestational age or with a birth weight of more than 1500 g followed up in the unit during the same period, discharged from the unit and reached to the adjusted age of 1-3 years. Preterm infants who had severe cardiopulmonary problem, who were lost in the first day of life and who had significant anomaly were excluded from the study. A total of 640 infants who were born before the 37th gestational age were followed up in the neonatalology unit during the study period. 165 of these infants (25%) were born before the 32nd gestational age and 475 (75%) were born at the 33-36th gestational age. 120 (73%) of the infants who were born before the 32nd gestational age were discharged and 462 (97.3%) of the infants who were born at the 33-37th gestational age were discharged. First of all, the families of infants who were born before the 32nd gestational age were called for invitation to the study, but only 47 could be reached, since most families were officers and soldiers and were assigned to other provinces. 35 of these (30%) gave consent for the study. Preterm infants in the control group (n=56) were invited by selecting among preterm infants followed up during the same period as the study group. Families were informed about the study. Written informed consent and local ethics committe approval (TÜTFEK 2008/083) were obtained.

Prenatal, natal and postnatal information of all subjects were obtained retrospectively from hospitalization files, history taken from the families, patient follow up records of the mother and epicrisis information of the patients who were not born in our hospital and referred from outside.

In the prenatal history, maternal age, maternal diabetes, preeclampsia, eclampsia, chronic hypertension, premature rupture of membranes, chorioamnionitis, prenatal bleeding, presence of multiple pregnancy, tocolysis, prenatal steroid administration, adequacy of the amniotic fluid and Doppler blood flow studies were investigated.

In the perinatal history, time of rupture of membranes, mode of delivery, place of birth, APGAR scores, need for resuscitation, gender, birth weights, height and head circumference were determined. Following delivery gestational ages of the newborns were determined using Ballard scoring system in accordance with physical and neurological criteria (10). Newborns were defined as AGA (appropriate for gestational age), SGA (small for gestational age) or LGA (large for gestational age) according to intrauterine growth in concordance with the gestational age and birth weights on the Lubchenco curve (11). Problems of newborns which developed during the follow up period including "respiratory distress syndrome" type 1 (RDS type 1) (12), bronchopulmonary dysplasia (BPD) and its severity (13), patent ductus arteriosus (PDA), IVB (14), presence of periventricular leucomalacia, retinopathy of prematurity (ROP) (15), necrotizing enterocolitis (NEC) (16), need for phototherapy and definite sepsis (17) were determined. Each night spent in the unit was calculated as the hospitalization period.

Families who accepted to participate in the study and their babies were welcomed by a pediatrician who did not know in which group the newborns were. Growth measurements (height, head circumference, weight) were done and complete physical examination was performed. Afterwards, the families completed the questionnaire form. The questionnaire included questions about socioeconomic level, general well-being, visual and auditory function and motor and language development. In terms of the social status of the child, the place of birth (village/town), whom the child was brought up by, how many siblings the child had, the education level and occupation of the parents were interrogated. The socio-economic status scale (SED) was used to determine the socioeconomic status of the families (18).

Afterwards, psychiatric examinations of the children were performed in the Child and Adolescent Psychiatry outpatient clinic and the Brief 1-3 Age Social Emotional Assessment Scale was completed. The Brief Symptom Inventory was used for the mothers. The Denver Developmental Screening Test (DGTT) was performed without being aware of the age of the subjects (19,20).

For social and emotional evaluation of the subjects the Brief 1-3 Age Social and Emotional Assessment Scale-Turkish (K-1/3-SDD-TR) was applied (21). This scale is the Turkish version of the scale (22) which was developed to screen the severity of pysichiatric symptoms and pysichosocial development problems. The scale is made up of a total of 42 items 31 of which evaluate pysichiatric problems and 11 of which evaluate pysichosocial development. Each item is scored with one of the three options (0: not true/rarely; 1: partially true/sometimes; 2: rather true/frequently).

A higher pysichiatric problem score reflects a higher level of pysichiatric problem and a higher pysichosocial development score reflects a higher level of pysichosocial development.

To evaluate the emotional state of the primary caretakers (mothers) of the subjects the Brief Symptom Inventory (BSI) was used (23). The score range of this scale ranges between 0 and 212. As the score gets higher, the frequency of emotional problems increases. The evaluation which shows the actual functionality of the Brief Symptom Inventory is the Global Severity Index (GSI).

Data analysis

Data of Group 1 and Group 2 were compared statistically. Data were given as mean ±SD, median, the lowest-the highest value or the number of subjects (%) according to the statistical test applied. When evaluating the data of the study, t-test or Man Whitney U test was used for samples independent of single-tail analyses by evaluating the normal distribution of the data for comparing qualitative data. In comparison of quantitative data between the two groups, chi-square test was used. Spearman test was used for correlation analysis. Minitab Release 13 program was used for statistical evaluation. A p value of <0.05 was considered to be significant.

Results

The study group (group 1) included 35 subjects and the control group (group 2) included 56 subjects. When the two groups were compared in terms of prenatal, natal and postnatal properties, the presence of preeclampsia in the mothers was found with a higher rate (p=0.009), body weigth was lower (p<0.001), the rate of being SGA was higher (p=0.002), APGAR scores at the 1st and 5th minute were lower (p<0.001, p<0.001, respectively) in group 1 compared to group 2. In addition, subjects in group 1 were born by normal vaginal delivery with a higher rate (p=0.011), received the diagnoses including RDS type 1 (p<0.001), chronic lung disease (p=0.001), NEC (p<0.001), sepsis (p=0.003), apnea (p<0.001), IVB (p=0.004) and ROP (p=0,002) with a higher rate and stayed in the hospital for a longer time (p<0.001) (Table 1).

When the subjects were seen at the corrected age of 1-3, the subjects in group 1 were at a mean age of 21±8 months

Table 1. Prenatal and postnatal properties of the groups

	Group 1 (≤32 gestational week) (n=35)	Grup 2 (>32 gestational week) (n=56)	p
Maternal diabetes, n (%)	1 (3)	7 (12.5)	>0.05
Preclampsia, n (%)	16 (46)	11 (20)	**0.009**
PROM, n (%)	12 (34)	15 (27)	>0.05
Chorioamnionitis, n (%)	6 (17)	4 (7)	>0.05
Maternal smoking, n (%) **Antenatal steroid, n (%)**	2 (6)	1 (1.8)	>0.05
Multiple pregnancy, n (%)	18 (51)	24 (43)	>0.05
Gestational week*#	29.6 ± 1.6 27-32	35± 1.3 33-37	**<0.001**
Gender (M) n (%)	20 (57)	36 (64)	>0.05
Birth weight*#	1032 ± 204 710-1470	2166±450 1370-3400	**<0.001**
AGA, n (%) **SGA, n (%)**	19 (54) 16 (46)	49 (88) 7 (12)	**0.002**
Mode of delivery, cesarean (%)	28 (80)	54 (96)	0.011
Birth place (TUMF), n(%)	29 (83)	49 (88)	>0.05
Apgar at the first minute#	2-9	0-9	**<0.001**
Apgar at the 5th minute#	3-10	2-10	**<0.001**
RDS Type 1, n(%)	31 (89)	15 (27)	**<0.001**
Surfactant treatment, n(%)	30 (86)	15 (27)	**<0.001**
CLD n(%)	20 (57)	1(2)	**<0.001**
Ventilator dwell time (days)*#	7.8 ±12.6 1-60	3±2.3 1-6	>0.05
Postnatal steroid treatment, n(%)	22 (63)	-	
Sepsis, n(%) **Definite** **Suspicious**	 2 (6) 14 (40)	 1 (2) 4 (7)	 **0.003**
Apnea, n(%)	31 (89)	8 (14)	**<0.001**
NEK, n(%)	31 (89)	7 (12.6)	**<0.001**
ROP, n(%)	15(45)	-	**0.002**
IVB, n(%)	10 (29)	-	0.004
Nutrition type: **Breast milk, n(%)** **Preterm formula, n(%)** **Breast milk+Preterm formula, n(%)**	 18 (52) 4 (11) 13 (37)	 27(48) 3(5) 26 (47)	 >0.05
Hospitalization time*	60.4 ±23	12±11	**<0.001**

*mean ± SD, # the lowest – the highest, PROM:premature rupture of membranes, CLD: chronic lung disease, NEC: necrotizing enterocolitis, ROP: retinopathy of prematurity, IVB: Intraventricular bleeding , AGA: appropriate for gestational age, SGA: small for gestational age

and the subjects in group 2 were at a mean age of 19±6 months and their ages were statistically similar. The socioeconomic states of the subjects were found to be statistically similar.

No difference was found between the education levels of the mothers, while the education levels of the fathers in group 1 were significantly lower compared to group 2 (p=0.002) (Table 2).

An abnormal Denver developmental test was found with a higher rate and the rate of neurological developmental delay expressed by the family was statistically higher in group 1 compared to group 2 (p=0.001, p<0.001, respectively). On the other hand, according to the results of "the Brief 1-3 Age Social Emotional Assessment Scale" applied to the groups, the mean PS score was found to be 10.12±4.7 in group 1, while mean PS score was found to be 9.8±5 in group 2 and the difference was not statistically significant. The mean pyschosocial development score was found to be 17±4.3 in group 1 and 18.6±3 in group 2 and the difference was found to be statistically significant (p=0.04). While a moderate inverse relation was found between the psychiatric problem score and gender (r=-0.334, p=0.002), a moderate linear relation was found between the pyschosocial development score and gender (r=0.282, p=0.009). While the pyschiatric problem score was found to be higher in boys compared to girls (11.2±5.1 vs 7.8±3.5; p=0.002), pyschosocial development was found to be better in girls (18.9±3.4 vs 17.24±3.6; p=0.038). While no relation was found between socioeconomic level, maternal age, maternal education, hospitalization time and pyschiatric problem scores, the shorter the hospitalization time was, the higher pyschosocial development scores were found (r=-0.33; p=0,002). Low pyschodevelopmental score was found to be related to history of developmental delay given by the mother (p=0.021). While no relation was found between the pyschiatric problem score and IVB, it was found that pyschosocial development score was lower in children with IVB (p=0.049). It was found that the higher pyschodevelopmental score was, the higher was the possibility of a normal Denver developmental test result (r=-0.3; p=0.004). When the Global Severity Index (0.61±0.44 & 0.66±0.64), the Symptom Total Index (18.4±10.6& 19±13.4) and the Symptom Global Index (1.5±0.7&1.5±0.57) in the Brief Symptom Inventory applied to mothers of the subjects were examined, no difference was found between the groups. The Symptom Global index was above the value of 1.5 in 51.4% of the mothers in group 1 and in 40% of the mothers in group 2 and the difference was not statistically significant.

Discussion

In this prospective, controlled study where we made developmental and pyschiatric evaluations in very premature infants and moderately-borderline premature infants comparatively, outcomes of abnormal neurodevelopment was found with a higher rate and pyschosocial development score was found to be lower in very premature infants, while no difference was found in pyschiatric problem scores. When preterm or SGA newborns were compared with term newborns, many studies have shown that they had increased risk in terms of motor, cognitive and behavioral disorders (24-27). There are few studies evaluating developmental and pyschiatric outcomes of children who are born very prematurely at a young age like 3 years and comparison with term newborns have been made in most of these studies and different scales have been used for evaluation. Although the Brief 1-3 years of Age Social

Table 2. Socio-demographic properties of the groups

	Group 1 (≤32 gestational week) (n=35)	Group 2 (>32 gestational week) (n=56)	p
Maternal age*	28±5.8	30±8	>0.05
Paternal age*	32±5.7	33.6±8	>0.05
Maternal education, n(%)			
University	3 (8)	17 (30)	
High-school	10 (29)	13 (23)	>0.05
Secondary school	2 (6)	8 (14)	
Primary school	13 (37)	17 (30)	
Illiterate	-	-	
Paternal education, n(%)			
University	3 (8)	19 (34)	
High-school	8 (23)	19 (34)	0.002
Secondary school	5 (14)	2 (4)	
Primary school	19 (55)	14 (28)	
Illiterate	-	-	
SEL scale, n(%)			
Very well	5 (14)	10 (18)	
Good	6 (17)	18 (32)	>0.05
Moderate	10(29)	14(25)	
Poor	14(40)	14(25)	

SEL: socoeconomic level scale,* mean ± SD, # The lowest – the highest

Table 3. Neurodevelopmental and pyschosocial properties of the groups			
	Group 1 (≤32 gestational week) (n=35)	**Group 2 (>32 gestationaal week) (n=56)**	**p**
Postnatal adjusted age (months)*#	23±9 (12-36)	19.8±6.7 (12-36)	>0.05
DDST, n(%)			**0.001**
Normal	7 (20)	25 (45)	
Suspicious	15 (43)	26 (46)	
Abormal	13 (37)	5 (9)	
Developmental delay (according to the parents) n(%)	23 (66)	5 (9)	**<0.001**
Social-emotional assessment scale			
Pyschiatric problem score	10.12±4.7	9.8±5	>0.005
Pyschosocial development score	17±4.3	18.6±3	**0.04**

DGTT: Denver Gelişim Tarama Testi

and Emotionaal Assessment Scale-Turkish (K-1/3-SDD-TR) which we used for social and emotional assessment of our subjects in our study was the Turkish version of the scale developed by Briggs-Gowan et al.(22) and was reported to show good relation with behavioral assessment scale (CBLC/1.5-5) which was used in the above-mentioned studies, the fact that comparison was made with moderate-borderline premature newborns instead of term newborns may cause difference in the pyschiatric problem score or these problems will develop in the later age periods.

Hartman et al.(28) found the neurodevelopmental risk examination scores to be high in 11% of a group of infants who were born before the 32nd gestational week. This is related with exposure of the newborn baby to events which include need for mechanical ventilation, acidosis attacks, hypoglycemia, sepsis, convulsion and transfontanel ultrasound findings and which would result in brain cell damage. In recent studies, the relation of brain demage with white matter anomalies which develop postnatally was shown and deficiencies in cognitive and motor development determined at the age of two in preterm children were related to decreased volume of hypoccampus (28,29). In studies which evaluated neurodevelopmental and neurobehavioral state of infants who were born before the 32nd gestational week, it was reported that these infants had abnormal neuromotor development and this abnormality was a predictor of school problems in the future years which were similar to our findings (30). In our study, APGAR scores at the first and 5th minute were lower, the rate of being SGA was higher, the rates of diagnoses including BPD, NEC, IVB, ROP and apnea were higher in infants who were born before the 32nd gestational week compared to the infants who were born after the 32nd gestational week and these infants were found to have stayed longer in the hospital. Exposure of these infants to severe medical complications supports the wiew that central nervous system demage may develop, as stated in the references. Another finding supporting this is the fact that abnormal results were found with higher rate in infants who were born before the 32nd gestational week on the DDST applied to the groups.

However, medical risk factors are responsible of only a part of these long-term outcomes (31). External factors including social class, parental education level, marital status, familial structure and function, the pyschological state of the parents and home environment have been suggested to be related to the developmental outcomes of the newborns (32). In our study, no difference was found in terms of maternal education level between very premature newborns and moderate-borderline premature newborns, while paternal education level was found to be lower in the first group. Socioeconomic levels were statistically similar. In addition, the Global Severity Index, the Symptom Total Index and the Symptom Global Index were not found to be different in the Brief Symptom Inventory applied to mothers. While it was found that the pyschiatric problem score was found to be higher in boys and the pyschosocial problem score was found to be high in girls, it was interesting that no relation could be found between socioeconomic level, maternal education, gestational week and pyschiatric problem scores and pyschosocial development scores. In a study evaluating if perinatal and neonatal events explained the disadvantage in boys during the early childhood by affecting gender-specific responses at the adjusted age of 18-22 months in approximately 2500 newborns who were born before the 18th gestational week, it was suggested that boys carried a higher hereditary risk and unmeasurable biological variables probably rendered preterm boys disadvantageous in terms of neurodevelopmental outcomes (33). Similarly, in a study where neurodevelopmental evaluation was done at the adjusted age of 18-22 months in approximately 5000 very small for gestational age (<=1000 g) live births, single delivery, higher birth weight, absence of neonatal diseases, presence of private health insurance, white race and female gender were found to be related to the possibility of normal neurodevelopmental outcome (34). We could unfortunately not perform multi-variant regression analysis to determine medical or paramedical independent variables which affect abnormal developmental and pyschiatric outcomes because of inadequate number of subjects. This condition which causes an important limitation in

our study arises from the fact that the follow up rate in the study group was low (30%). Although no significant difference was found between preterm newborns who presented and did not present for follow-up in terms of gestational age, the rate of being SGA, BPD, IVB and hospitalization time, increased risk in terms of behavioral problems may be present or developmental problems may be observed with a lower rate in the subject who did not present for follow-up.

The same may be valid for developmental assessments of the mothers/ parents and for the Global index results. Therefore, it seems not possible to exclude the possibility that the results may be erroneous. However, we believe that our study is valuable in terms of reflecting short-term and long-term outcomes of very premature infants in our region. We are planning to perform further studies increasing the number of subjects and the rates of follow-up. Thus, it will be possible to give consultancy service to the parents of premature infants who carry a risk of severe and mild neurodevelopmental deficicencies which may affect academic, behavioral and social function negatively in the future and it will also be possible to educate the team who follows the child and to constitute early intervention programs.

Conflict of interest: None declared.

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