THE NEW ARMENIAN MEDICAL JOURNAL
Vol.9 (2015), No 4, p.61-68

NEURODEVELOPMENTAL OUTCOME OF VERY LOW BIRTH WEIGHT INFANTS AT 2 YEARS OF CORRECTED AGE

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Received 04/24/2015; accepted for printing 08/22/2015

Abstract

***Objectives**: To investigate the development of very low birth weight preterm infants at 2 years of corrected age and find correlations between neonatal characteristics and neurodevelopmental outcomes.*

Methods: The subjects of the study were ex-premature neonates with very low birth weight (≤ 32 weeks, ≤1500 g). Neurodevelopmental outcome was assessed using Bayley scale of infant development.

***Results**: It was possible to assess neurodevelopmental outcomes in 58 ex-premature infants during study period. Mean birth weight was 1340 g, gestational age was 30 weeks, female and male ratio – 1:1.5. From investigated patients 74% had average and high average level of motor development, 93% – average and high average level of mental development and 64% - average and high average level of speech development. Borderline and extremely low motor development was found in 9% of infants and the same level of speech development – in 13% of infants. Neither of studied infants had mental retardation of severe degree. More than 10% had borderline and extremely low levels in socio-emotional and adaptive-behavioral developmental domains. Fine motor problems were developed in 5% of patients, gross motor problems – 10%. Generally only 9% had motor problems using composite scores. Five percent had some mental problems (low average level). Expressive area of speech development is much more affected than receptive one (24% vs. 5%). Socio-emotional and behavioral problems were more frequent, especially in social and practical areas (27% and 25%, respectively). Sixty four percent of ex-premature infants have completely normal development, 9% have only cerebral palsy, 21% – only speech delay and 4% - different types of developmental problems. General hypotonia was diagnosed in 31%, muscular hypertonia in 12% and normal muscular tonus was found in 57% of examined patients during neurological observation. Mechanical ventilation during neonatal period, as well as deviations during neurosonography (2nd grade interventricular haemorrhage, cystic periventricular leucomalacia, ventriculomegaly at full-term age and widening of extracerebral and intrahemispheric space), are risk factors for later developmental deviations.*

***Conclusion**: Bayley scale of infant development is a suitable standardized test for the assessment of infant development by qualitative and quantitative descriptions. Cerebral palsy rate was 9% in cohort study. Speech problems (especially expressive type of delay) and socio-emotional and behavioral problems are more frequent than motor problems. About two third of very low birth weight infants have completely normal development during early childhood.*

***Keywords:** prematurity, neurodevelopment, Bayley Scale of Infant Development, motor problems.*

Introduction

Preterm birth is a serious worldwide perinatal medical problem, not only in terms of mortality, but also in relation with short- and long-term morbidity and financial implications for health-care systems. Although the number of live-born registered in most industrialized nations have remained relatively stable in recent years, the incidence of preterm birth (birth earlier than 37 completed weeks of gestation) and of low birth weight (birth weight less than 2500 *g*) has increased [*Lumley J, 2003; Tucker J, McGuire W, 2004; Petrou S, 2005; Goldenberg R et al., 2008*].

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The shorter the gestation, the smaller the baby and the higher the risk of death, morbidity and disability. Survival rate among these vulnerable infants has improved considerably throughout the 1990s. The problem of long-term outcomes in extremely premature survivors (birth at less than 32 completed weeks of gestation) occurred with the improvement of survival rates. Adverse effects of neurodevelopment in early childhood include global developmental delay, cerebral palsy, blindness and deafness in early childhood., Ex-premature children in early and adolescence age are at increased risk of unfavorable mental health outcomes if taking into account these neurosensory and cognitive problems [*Hagberg B et al., 1989; Pharoah P et al., 1990; Hagberg B, Hagberg G, 1993; Schothorst P, van Engeland H, 1996; Stewart A et al., 1999; Huddy C et al., 2001; Larsson H et al., 2005; Platt M et al., 2007*]. Clear characterization of emotional and behavioral outcomes of preterm birth may offer the opportunity for interventions that improve prognosis, both in neonatal intensive care unit and after discharge.

Preterm infants born before 32 weeks of gestation with very low birth weight (less than 1500 *g*) are at high risk for a range of neurodevelopmental disorders including cerebral palsy (CP) and sensory, cognitive, and behavioral disabilities. CP is a neurodevelopmental motor condition that can be recognized from early childhood. Its prevalence has decreased or at least leveled off over the last decade [*SCPE, 2000; Saigal S, Doyle L, 2008; Himmelmann K et al., 2010; van Haastert I et al., 2011*].

There are several methods for the assessment of infant development [*Griffiths R, 1954; 1996; Koot H et al., 1997; Ostrander R et al., 1998; Kelly Vance L et al., 1999; Achenbach T, Rescorla L, 2000; Gladstone M et al., 2010; Khan N et al., 2010*]. The Bayley scale of infant development is an individually administered instrument that assessed the development of children from 1 month to 42 months of age [*Bayley N, 2006*]. It is a standard series of measurements originally developed by psychologist Nancy Bayley used primarily to assess the motor (fine and gross), speech (receptive and expressive), and cognitive development of infants. This measure consists of a series of developmental play tasks and lasts 45 - 60 minutes [*Weiss L et al., 2010*].

Beyley scale is used to identify suspected developmental delay in children consistent with current scholarship on child development, to assist in intervention planning and other important clinical services. Additionally, the Bayley-III is designed to promote the understanding of a child's strength and weakness in relation to five developmental domains: mental, speech, motor, socio-emotional and adaptive-behavioral [*Black M, Matula K, 1999*].

The aim of study was to investigate the development of very low birth weight infants in 5 main domains (motor, mental, speech, socio-emotional and adaptive-behavioral) at 2 years of corrected age and to find correlations between perinatal, neonatal, neurosonographic characteristics and neurodevelopmental outcomes.

Materials and methods

The subjects of present study were ex-premature neonates with very low birth weight (less than 1500 *g*) with gestational age of less than 32 weeks. The neonates were treated in intensive care units of 3rd level, in 2 medical centers of Yerevan city: Scientific Research Centre of Maternal and Child Health Protection and the Institute of Reproductive Health, Perinatology, Obstetrics and Gynecology from February to December 2012. The parents of infants were informed about the study and written parental consent was obtained.

Individual neurodevelopmental outcome in children was assessed using Bayley scale of infant development (BSID-III) at 2 years of corrected age [*Black M, Matula K, 1999*].

During study period 100 very low birth weight infants who had undergone serial cranial ultrasound exams were treated in neonatal care units. From those 100 infants, 20 (20%) didn't survived during neonatal period. It wasn't possible to continue further follow-up of 22 patients from survived 80 infants. In 58 patients the study was conducted with the use of Bayley scale of infant development at 2 years of corrected age.

Examined ex-premature infants' mean birth weight was 1340 *g* (min 740 *g*, max 2000 *g*; SD = 303*g*) and mean gestational age was 30 weeks (min 26 weeks, max 34 weeks; SD = 1.7 week). Female – male ratio was 1:1.5.

The correspondence between qualitative and quantitative characteristics of developmental levels is shown in Table 1.

Statistical analysis was performed with IBM

SPSS Statistics 20. Fisher's exact test (2-sided) was used for categorical variables and Mann-Whitney test for quantitative variables, $p < 0.05$ indicated a significant difference.

Results

The development of infants was assessed using qualitative descriptions. The correspondence between qualitative and quantitative characteristics of developmental levels is shown in Table 1. So, if the composite score of a child in any domain is 75 or 125, than his/her qualitative description is "borderline" or "superior", respectively. Using this approach, graphic depictions were made which are presented in figure 1 and 2 to show main categories of developmental outcomes. As it can be seen in graphics, 74% of infants had average and high average level of motor development, 93% – average and high average level of cognitive development, and 64% - average and high average level of speech development. Borderline or extremely low motor development was found in 9% of infants (children with cerebral palsy), and the same level of speech development in 13% of infants. None of infants had mental retardation of severe degree (only 5% had low average level of mental development).

Table 1.

Qualitative descriptions of composite score and its equivalents

Composite score or its equivalent	Classification
130 and higher	Very superior
120-129	Superior
110-119	High average
90-109	Average
80-89	Low average
70-79	Borderline
69 and low	Extremely low

Socio-emotional and adaptive behavioral developmental domains are mentioned in figure 2, in which the number of children with superior, very superior, borderline or extremely low levels of development.

Developmental problems were found in examined children while using quantitative descriptions, which are shown in table 2. Scale scores less than 7 and composite scores less than 85 are evidence of developmental retardations in appropriate domains and subdomains.

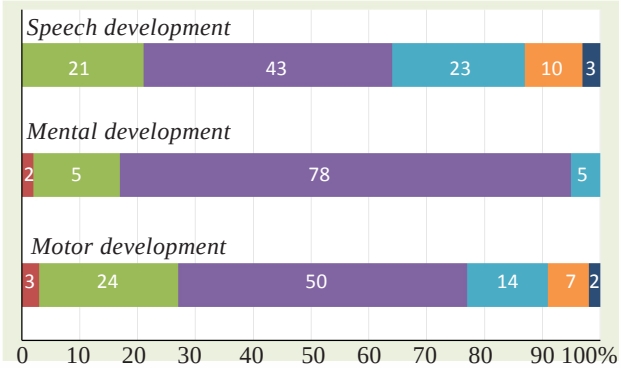

Figure 1. *Qualitative descriptions of 3 developmental domains (%).*
Notes: Levels: red – superior, green – high average, purple – average, turqoise – low average, orange – borderline, dark blue – extremely low.

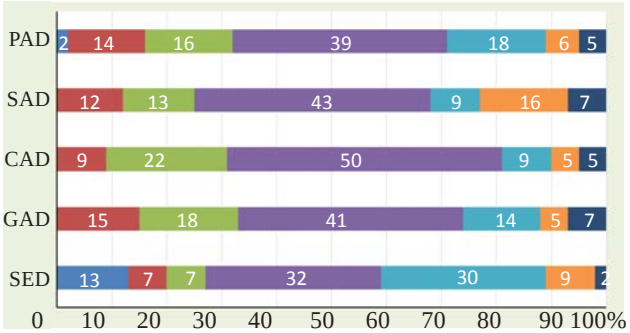

Figure 2. *Qualitative descriptions of socio – emotional and adaptive - behavioral developmental domains in children (%)*
Notes: *Light blue – very superior, red – superior, green – high average, purple – average, turqoise – low average, orange – borderline, dark blue – extremely low. PAD – practical – adaptive development, SAD – social –adaptive development, CAD – conceptual –adaptive development, GAD – general adaptive development, SED – socio –emotional development.*

So, fine motor problems were developed in 5% of patients, gross motor problems – 10%. Generally only 9% had motor problems using composite scores. Five percent had some mental problems. Expressive area of speech development is much more affected than receptive one (24% vs. 5%) causing speech delay in 21%. Socio-emotional and behavioral problems were more frequent, especially in social and practical areas (27% and 25%, respectively).

The whole picture of studied children development is shown in table 3. So 64% of ex-premature infants have completely normal development, 9% – only cerebral palsy, 21% – only speech delay and 4% – different types of developmental problems.

Table 2.

Developmental problems found while using Bayley-III scale

Domain	Problems	%
Motor problems	gross motor	10
	fine motor	5
	composite score	9
Mental problems	deficit	5
Speech delay	receptive	5
	expressive	24
	composite	21
Socio-emotional	problems	23
Behavioral development	general adaptive	16
	conceptual – adaptive	14
	social – adaptive	27
	practical – adaptive	25

Table 3.

Developmental characteristics of studied patients (n=58)

Development	%
Normal development	64%
Only speech delay	21%
Cerebral palsy	9%
Cerebral palsy combined with speech problems	1.5%
Non-CP motor problems	1.5%
Cognitive and severe speech delay	1.5%
Deafness, absence of speech, motor and cognitive delay	1.5%

One patient had a problem of speech development because of bilateral deafness due to congenital cytomegalovirus infection.

From 58 examined patients 9 (14%) had motor problems. From those 6 diagnosed as having cerebral palsy, 1 had motor delay due to congenital cytomegalovirus infection, and 1 had non-CP motor problems (some neurological deviations in tonus, awkwardness of fine and gross motor). Two mentioned patients without CP, but with motor problems also had fine motor difficulties. From CP cases 3 had left spastic hemiplegia, other 3 had spastic quadriplegia. Three patients (2 with hemiplegia and one with quadriplegia) could sit and walk independently, the others could not walk even with support. Only one patient with CP had fine motor problems. Patients with motor problems have also mental delay in 13% of cases, speech problems in 25%, socio-emotional problems in 25% and behavioral problems in about 50% of cases.

General hypotonia was diagnosed in 31%, muscular tonus in 12% and normal muscular tonus was found in 57% of examined patients during neurological observation.

Using statistical methods, an attempt of identification of any risk factors causing developmental problems was initiated. Statistically significant associations (p-value less than 0.05) between neonatal characteristics, cranial ultrasound findings and developmental problems are presented in table 4. Need for mechanical ventilation is risk factor for later CP and speech delay ($p = 0.023$), 2nd grade interventricular haemorrhage, cystic periventricular leucomalacia were associated with CP cases ($p = 0.017$), ventriculomegaly at full-term age and widening of extracerebral and interhemispheric space were predictors for CP and speech delay ($p<0.05$).

Discussion

Survival of very low birth weight infants continues to improve, but long-term neurodevelopmental outcomes continue to be a problem.

Mental and motor development is usually assessed using the Bayley scale of infant development. Bayley-III is a good standardized test for the assessment of infants' development by qualitative and quantitative descriptions. Children with severe mental disorders during early assessment will have persistent severe disorders later. On the other hand, early assessment of non-severe disorders does not confidently predict good state at later age [*Bayley N, 1993*].

Many preterm children demonstrate mild fine or gross motor delay, mild but persistent neuromotor abnormalities, motor planning problems and/or sensorimotor integration problems that lead to functional disorders, academic difficulties and socio–emotional problems [*Schmidhauser J et al., 2006; Behrman R, Butler S, 2007; Davis N et al., 2007; Fawke J, 2007; Marlow N et al., 2007*].

In a Swiss study of 6-year-olds, children with birth weight below 1500*g* had low scores on multiple motor tasks (especially quality and speed of

Table 4.

Correlations between neonatal characteristics, CUS findings and development

Risk factors	Motor problems (n=8)	Speech delay (n=13)	Normal development (n=37)	p*
Mechanical ventilation of lungs (total n = 3%)	2 (67)	1 (33)	0	0.023
2nd grade intraventricular haemorrhage (total n = 2%)	2 (100)	0	0	0.017
Cystic periventricular leucomalacia (total n = 2%)	2 (100)	0	0	0.017
Ventriculomegaly at full-term age (total n=12%)	5 (42)	4 (33)	3 (25)	0.007
Widening of extracerebral and interhemispheric space (total n = 20%)	6 (30)	10 (50)	4 (20)	0.041

Note*: *Fisher's exact 2-sided test, p <0.05 was considered significant.*

movements) [*Schmidhauser J et al., 2006*]. Scores are correlated with brain injury during neonatal ultrasound surveys and neurological disorders at 6 years of age. It should be mentioned that preterm infants with no neurological disorders had lower scores in comparison with than the population of healthy full-term children.

In the present study, the prevalence of abnormal development in mental, motor, speech, socio-emotional and adaptive-behavioral areas was 5, 9, 21, 23 and 27%, respectively, which is comparable with published data from Brazil (7, 7, 30, 28 and 38%, respectively) [*Fernandes L et al., 2012*]. The frequencies of disorders were lower in cognitive and motor areas and similar in speech while comparing with those reported by Anderson P and co-authors (2010). The lower frequency of cognitive and motor disorders may be due to the lower gestational age and birth weight observed in the present study.

Although many preterm infants demonstrate neuromotor abnormalities during the observation, most of them do not develop cerebral palsy [*Dolk H et al., 2006; Fawke J, 2007; Marlow N et al., 2007]*. Rates of cerebral palsy in infants born after 1990s range from 4% to 12% for survivors with birth weight below 1000*g*, 6% to 20% for infants born before 27 weeks gestation, and 21% to 23% for infants born before 25 weeks gestation [*Behrman R, Butler S, 2007*]. Cerebral palsy prevalence was 1.2 per 1000 live births for birth weight over 2499*g*, 11.3 for birth weight 1500–2499*g* and 44.5 for 1500*g* in children born 1994–1997 in Northern Ireland [*Dolk H et al., 2006*]. Mortality is high in infants with birth weights below 1000*g*, so cerebral palsy developed in 47 per 1000 live births and 99.5 per 1000 (9.9%) survivors.

In 2008, Larroque B and co-authors reported the results of the EPIPAGE Study regarding the outcome at 5 years of children born at < 33 weeks. Cerebral palsy was diagnosed in 9% of children born very preterm [*Larroque B et al., 2004*]. Another study done in India shows, that very low birth weight babies at 1 year of corrected age had CP in 3% of cases, 3% had suspected abnormality (mild hypotonia), 11% had gross motor and 8% had language abnormality [*Mukhopadhyay K et al., 2010*].

Recent studies have not only confirmed that children born preterm have more cognitive disorders and academic difficulties than full-term controls, but they also suggest that these are more common than motor, visual or hearing disorders [*Kirkegaard I et al., 2006; Behrman R, Butler S, 2007; Marlow N et al., 2007; Sommer C et al., 2007; Wilson-Costello D et al., 2007*]. In a study of 2-year-olds, 54% of children born before 27 weeks gestation had a Griffith Mental Developmental Quotient greater than 2 standard deviations below the mean; only 40% had normal mental abilities [*Sommer C et al., 2007*]. It should be mentioned that no significant changes in cognitive tests' results were registered while comparing children born with birth weight below 1500*g*, conducted in 1982 [*Wilson-Costello D et al., 2007*].

In addition to birth weight and gestational age, factors associated with cognitive outcomes include neuroimaging evidence of brain injury, neuromotor abnormalities during the observation, specification

of male gender and some factors related to severity of neonatal illness or chronic lung disease [*Kirkegaard I et al., 2006; Behrman R, Butler S, 2007; Marret S et al., 2007; Sommer C et al., 2007*]. Serial head ultrasounds are a valuable bedside tool for following brain development in even the sickest preterm infants [*Anderson N et al., 2006; Broitman E et al., 2007; Chuang Y et al., 2007; Leviton A et al., 2007; Narberhaus A et al., 2007*]. As many as 39% of children with normal head ultrasounds had neurodevelopmental impairment.

Mechanical ventilations during neonatal period, as well as several CUS abnormalities (2nd grade interventricular haemorrhage, cystic periventricular leucomalacia, ventriculomegaly at full-term age and widening of extracerebral and intrahemispheric space) are risk factors for later developmental deviations according to the present study.

The importance of knowledge about neurodevelopmental outcome is the key for the development of better treatment strategies.

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