tat că într-o 1 lună cifrele TA au atins valori normale în 29,7% din cazuri, după 3 luni – în 53,8% din cazuri, iar după 6 luni – în 58,8% din cazuri, dintre care mai frecvent copiii care au urmat tratament medicamentos şi au dat dovadă de o complianță bună a tratamentului administrat.

2. Cifrele TA, după 6 luni, s-au micşorat până la limitele normei în 33,3% din cazuri printre copiii care au urmat tratament nonmedicamentos şi în 76,7% din cazuri printre copiii care au urmat tratament medicamentos.
3. Dinamică negativă a cifrelor TA a fost atestată în 42,1% cazuri din totalul copiilor hipertensivi, mai frecvent la copiii cu complianță joasă a tratamentului administrat ($p<0,05$).

Bibliografie

1. Alonso A, Beunza J., Delgado-Rodríguez M. et al. Low-fat dairy consumption and reduced risk of hypertension: the Seguimiento Universidad de Navarra cohort. În: Am J Clin Nutr 2005; 82:972–979.

2. Appel L. Giles T., Black H. et al. Position Paper: dietary approaches to lower blood pressure. În: J Clin Hypertens 2009; 11:358–368.

3. Mu J., Liu Z., Liu W. et al. Reduction of blood pressure with calcium and potassium supplementation in children with salt sensitivity: a 2-year double-blinded placebo-controlled trial. În: J Hum Hypertens 2005; 19:479–483.

4. Nuñez-Cordoba J., Alonso A., Beunza J. et. al. Role of vegetables and fruits in Mediterranean diets to prevent hypertension. În: Eur J Clin Nutr 2009; 63:605–612.

5. Denzer C., Reithofer E., Wabitsch M. et. al. The outcome of childhood obesity management depends highly upon patient compliance. În: Eur J Pediatr 2004;163:99-104.

6. Couch S., Saelens B., Levin L. et. al. The efficacy of a clinic-based behavioral nutrition intervention emphasizing a DASH-type diet for adolescents with elevated blood pressure. În: J Pediatr 2008;152:494-501.

7. Alpert B. Excercise as a therapy to control hypertension în children. În: J. Sports Med 2000; 21 (suppl 2): S94- S96.

8. Lurbe E., Cifkova R., Cruickshank J. et al. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. In: Hypertension. 2009, 27(9), p. 1719-1742.

9. Flynn J. Hypertension in the young: epidemiology, sequelae and therapy. În: Editorial Review Nephrol Dial Transplant (2009) 24: 370–375.

10. Johann-Liang R., Wyeth J., Chen M. et. al. Pediatric drug surveillance and the Food and Drug Administration's adverse event reporting system: an overview of reports, 2003-2007. În: Pharmacoepidemiol Drug Saf. 2009 Jan;18(1):24-7.

11. Shahinfar S. A double-blind, dose-response study of losartan in hypertensive children. În: Am J Hypertens. 2005; 18: 183–190.

12. Matteucci M. Regression of left ventricular hypertrophy and normalization of myocardial contractility by ACE inhibition in children with CKD. În: Pediatr Nephrol 2007; 22:1459.

13. Assadi F. Effect of microalbuminuria lowering on regression of left ventricular hypertrophy in children and adolescents with essential hypertension. În: Pediatr Cardiol 2007, 28(1), p. 27-33.

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THE STAGES OF THE FOLLOW-UP SYSTEM DEVELOPMENT OF THE HIGH RISK PREMATURE BABIES. THE RESULTS OF NEURODEVELOPMENT OF PREMATURE BABIES DEPENDING OF THEIR BIRTH WEIGHT

Institute for Mother and Child Healthcare (director – Doctor in Medicine, Associate Professor Stefan Gatcan)

Summary

ETAPELE DEZVOLTĂRII SISTEMULUI DE DIAGNOSTIC ŞI SUPRAVEGHERE A NOU-NĂSCUȚILOR DIN GRUPURILE DE RISC ÎNALT. REZULTATELE NEURODEZVOLTĂRII COPIILOR ÎN FUNCȚIE DE GREUTATEA LOR LA NAŞTERE

Cuvinte-cheie. *Neurodezvoltare, supraveghere, nou-născut prematur, vârstă corectată.*

Actualitate. *Dezvoltarea sistemului de diagnostic şi supraveghere a nou-născuților din grupurile de risc a început din anul 2007 cu deschiderea şi înzestrarea cu echipament medical şi mijloace standardizate pentru evaluarea neurodezvoltării copiilor a Centrului de diagnostic şi supraveghere din incinta IMSP IMşiC, pregătirea personalului*

medical în subiectele de utilizare a acestor metode. Supravegherea nou-născuților din grupurile de risc pe parcursul primilor 2 ani de viață previne dereglările neurodezvoltării şi formelor severe a patologiei neurologice şi somatice. Deaceea scopul studiului a fost de a evalua neurodezvoltarea copiilor prematuri în dependență de greutatea lor la naştere la 2 ani de vârstă corectată.

Materiale şi metode. *Studiul s-a desfăşurat în perioada 1.01.2008 – 31.12.2010. Au fost analizate 155 fişe ale copiilor care au efectuat toate 6 vizite la centru: lotul I - 128 copii cu greutatea la naştere până la 1500g şi lotul II - 27 copii cu greutatea la naştere mai mare de 1500g. Supravegherea a inclus evaluarea neurodezvoltări cu ajutorul BSID-III, examenul neurologic, precum şi evaluarea sănătății somatice a copiilor.*

Rezultate. *Analiza morbidității a arătat diferențe statistic semnificative între loturi în direcția prevalării la copii din lotul I a cazurilor de hemoragii intraventriculare de gradul I şi II, leucomalacie periventriculară, convulsii, hipoglicemie, hiperbilirubinemie şi retinopatie a prematurului, comparativ cu copiii din lotul II. Analiza rezultatelor neurodezvoltării la 12, 18 şi 24 luni a relevat că la 2 ani vârstă corectată 71 (66,36%) din copiii lotului I şi 17 (73,91%) din copiii lotului II erau sănătoşi. Diferențe statistic semnificative în frecvența dereglărilor de neurodezvoltare de severitate medie între copiii din lotul I comparativ cu copiii din lotul II s-au observat numai la 12 luni ($p<0,05$). În lotul I copiii au avut mai frecvent dereglări severe de neurodezvoltare (total 13,08% pe seama paraliziei cerebrale, PC), comparativ cu lotul II (4,34%).*

Concluzii.

1. Severitatea cazurilor de neurodezvoltare la 2 ani vârstă corectată a fost mai exprimată la copiii din lotul I comparativ cu lotul II pe seama evoluției mai complicate a perioadei neonatale pe seama complicațiilor infecțioase (sepsis, meningită, enterocolită ulcero-necrotică), respiratorii (SDR) şi cerebrale (HIV, $p<0,05$, LPV, $p<0,05$ şi sindrom convulsiv, $p<0,05$) asociate cu prematuritatea.

2. Dereglările severe ale neurodezvoltării au prevalat la nou-născuții din lotul I în 13,08% (14) cazuri manifestate prin PC, hidrocefalie/ ventriculomegalie şi microcefalie, fiecare în 1,87% cazuri.

3. Printre domeniile neurodezvoltării la copiii lotului I au fost mai afectate funcțiile cognitive ($p<0.05$) şi expresive (limbaj) ($p<0.01$) manifestate prin retard mediu.

Резюме

ЭТАПЫ СТАНОВЛЕНИЯ СИСТЕМЫ ДИАГНОСТИКИ И НАБЛЮДЕНИЯ ЗА НЕДОНОШЕННЫМИ НОВОРОЖДЕННЫМИ ИЗ ГРУПП ВЫСОКОГО РИСКА. РЕЗУЛЬТАТЫ ПСИХОМОТОРНОГО РАЗВИТИЯ ДЕТЕЙ В ЗАВИСИМОСТИ ОТ ИХ ВЕСА ПРИ РОЖДЕНИИ

Ключевые слова. *Нейроразвитие, наблюдение, недоношенный новорожденный, скорректированный возраст.*

Актуальность. *Развитие системы наблюдения за новорожденными из групп высокого риска берет начало с 2007 года, когда был открыт и оснащен медицинским оборудованием и специальными стандартизованными инструментами Центр Диагностики и Наблюдения при НИИ МиР, были подготовлены медицинские кадры для использования этих техник. Наблюдение новорожденных из групп высокого риска в течение 2-х лет скорректированного возраста предупреждает нарушения психомоторного развития и развитие тяжелых форм патологии нервной системы и соматических заболеваний. В связи с этим целью исследования было изучить результаты нейроразвития у недоношенных детей, рожденных с массой тела <1500 г. и ≥1500 г. в возрасте 2-х лет скорректированного возраста.*

Материалы и методы. *Исследование было проведено в периоде с 1 января 2008 года по 31 декабря 2010 года. Были изучены истории 155 детей, которые посетили Центр 6 раз: 128 детей с весом при рождении менее 1500 г вошли в I группу и 27 детей с весом при рождении больше 1500 г составили II группу. Неврологическое наблюдение включало оценку неврологического статуса, психологическую оценку, производимую с помощью BSID (3-е издание), а так же оценку соматического здоровья ребенка.*

Результаты. *Анализ заболеваемости показал статистически значимое преобладание случаев внутрижелудочковых кровоизлияний, I и II степени, перивентрикулярной лейкомаляции, судорог, гипогликемии, гипербилирубинемии и ретинопании недоношенности у детей из I группы по сравнению со II группой. Анализ психомоторного развития в 12, 18 и 24 месяца показал, что к 2 годам 71 (66,36%) ребенок из I группы и 17 (73.91%) детей из II группы были здоровыми. Статистически значимые различия в частоте нарушений нейроразвития средней тяжести в I группе по-сравнению со II группой обнаружены только в 12 месяцев ($p<0,05$). В I группе преобладали тяжелые нарушения нейроразвития (всего 13,08% детей, из которых у 7,5% – детский церебральный паралич, ДЦП) по сравнению с группой II (4,34% детей ДЦП).*

Выводы.

1. Тяжесть нарушений нейроразвития в 2 года скорректированного возраста была более выраженной у детей из I группы по сравнению с II группой из-за осложненного течения неонатального периода за счет ин-

фекционных (сепсис, менингит, язвенно-некротический энтероколит), респираторных (СДР) и церебральных (ВЖК, p<0,05, ПВЛ, p<0,05; судорожный синдром, p<0,05) осложнений, связанных с недоношенностью.

2. Тяжелые нарушения нейроразвития преобладали у новорожденных с низким весом при рождении – в 13,08% (14) случаев представленные в 9,35% ДЦП, по 1,87% гидроцефалией/вентрикуломегалией и микроцефалией.

3. Среди психо-моторных функций у детей из группы I были наиболее нарушенными познавательные (p<0.05) и выразительные (языковые) (p<0.01) функции, выраженные в виде среднетяжелых нарушений.

The premature survival rates have increased tremendously with technological advances, but when compared with term births, prematurity and low birth weight (LBW) are among the most important predictors of infant morbidity and mortality. In the early 2000s survival rates have stabilized at approximately 85% for very low birth weight (VLBW, ≤1500 g) and 70% for extremely low birth weight (ELBW, ≤1000 g) infants [1, 2].

Neurodevelopmental disabilities and recurrent health problems take a toll in early childhood in these babies. Low birth weight babies are at a risk of poor growth, abnormal neurodevelopment, neurosensory impairment (hearing and vision) and later poor academic achievement and behavioral abnormalities due to occurrence of bronchopulmonary dysplasia (BDP), retinopathy of prematurity (ROP), intraventricular hemorrhage grade 3-4 (IVH) and periventricular leukomalacia (PVL) [3, 4].

In developed countries over the past 30 years, better perinatal, inclusively neonatal intensive care (aggressive resuscitation, surfactant and respiratory techniques as well as the nutritional management), has considerably improved the outcomes of premature babies their growth and neurodevelopment [5].

The Moldova Ministry of Health (MoH) has adopted the life birth registration of newborns starting with a birth weight of 500g and a gestational age of 22 weeks in its official state statistics according to the standards and criteria of the European Union since the 1st of January 2008. This initiative was supported by the implementation in neonatal intensive care of modern technologies for treating premature and sick children by the Moldovan-Swiss Perinatology Project (2006-2014). With the set-up and equipping of a "Diagnostic and Follow-up Centre" and the training of several doctors, a system of neurodevelopmental follow-up of premature babies was created in the republic in 2007, which has permitted the early detection and treatment of psychomotor sequels in newborns.

Post NICU Follow-up is the measurement of neurodevelopmental outcome after preterm birth and is the most important measure of NICU success [6]. Despite improving rates of survival for ELBW infants over the past two decades, the rate of disabilities has remained relatively constant, with up to 50% of these infants later exhibiting developmental disabilities such as motor, cognitive or behavioral impairments [7]. Five to fifteen percent will have cerebral palsy [1, 5, 8]. Differences between reported rates depend on variable rates of survival and neonatal complications, socio-economic status of the population reported on, reporting on chronologic versus corrected age, variability in the definition of disability or in its clinical diagnosis, the child's age at follow-up and variability in follow-up rates [6].

Developmental care is an intervention that focuses on environment and the infant, and is designed to minimize the stress of the infant in the neonatal intensive care environment (NICU) [9]. Several systematic reviews have shown variable short term benefits of developmental care, such as reduced oxygen dependency and improved neurodevelopmental outcomes up to 12 months; however, benefits were not sustained at two years [10]. Early intervention programs for preterm infants have a positive influence on cognitive outcomes in the short to medium term.

Though there is abundant literature available on follow up of high risk newborns and benefits on developmental care, there is scanty data of follow up from our country. Thus in this article we will describe the following: 1) stages of the neonatal Follow up service development and 2) neurodevelopmental outcomes of premature infants depending of their birth weight at 2 years corrected age.

Compartment 1. Stages of the neonatal Follow-up service development

There are following 3 stages of the service's development: stage of creation, stage of regionalization and strengthening and stage of its functionality regulation as part of the early intervention service.

Stage of creation. Republican service of neonatal diagnostic and follow up was founded in 2007-2008 at the Mother and Child Institute (MCI), when it was equipped with medical equipment (US machine, electroencephalograph, ophthalmoscope and audiometer) and standardized neurodevelopmental assessment tools; parallel there were organized trainings for medical staff on use of these tools, as well as on use of methods of specialized diagnostic examinations locally and abroad.

The process of creating the Follow-up service took place in parallel with the elaboration of the regulatory framework of its functioning and of related services, as well as of the standardized guidelines for provision of follow-up services for high-risk infants, hearing and vision screen protocols and informational materi-

als for medical staff and population (posters, leaflets) on these issues. Among the elaborated documents an important place is occupied by the Card on the baby's Follow-up, which is kept in family and is filled in by the doctor at each visit.

The service's development is part of Moldova's obligations set out in the Declaration on MDG achievement, as well as the measures stipulated in national policies and strategies until 2021. Operation of the service was approved by the MoH in 2010 and provides periodic follow up of infants discharged from NICU during the first 2 years of life. Taking into account the review of criteria of viability, the largest group of patients from the Follow up service is that of premature infants weighing up to 1500 g who are supervised until they reach 2 years corrected age. Follow up includes other categories of newborns with: severe intrauterine growth retardation, moderate or severe hypoxia (Sarnat grade II / III); IVH gr. III-IV and PVL; seizures, severe hyperbilirubinemia, infections of CNS and impaired neurological examination at discharge, and children requiring respiratory support.

Specialized services of these categories of children are provided in two subdivisions of the Center: monitoring and diagnostic.

Monitoring subdivision of children at risk of developing neurological sequels is basic and includes two offices: for premature babies and babies born at term with neurological diseases. Here the neuropediatrician is performing neurodevelopmental assessment through various standardized assessment procedures and techniques having in result the data on neurodevelopmental examination (general examination, level of alertness, activity, and responsiveness, primitive reflexes, evaluation of motor tone, posture, movements and deep tendon reflexes), speech and cognitive functions; behavior; hearing and visual assessment with fundoscopic examination; growth assessment. Neonatologist instructed in use of Bayley scales performs psychological assessment by using tests of screening neurodevelopmental BINS (Bayley Infant Neurodevelopment Screener) at 3 months and BSID-III (Bayley Scale of Infant and Toddler Development, third edition) starting from 3 months. Simultaneously the somatic state of the infant's health is examined; family history is collected, as well as antenatal, perinatal and postnatal history and socio-economic status of the family.

This subdivision has a database of children enrolled in the monitoring program, which counts from 2008 up to date 1265 children, of whom premature babies with birth weight less than 1500 g make up 527 (41,7%) of babies. The database includes the following compartments: epidemiological data, the status at birth and in the neonatal intensive care unit (NICU), the care received in NICU, the discharge and Follow up data. Compliance with the program of visits is ensured by active calling of children from home.

Diagnostic subdivision includes 3 offices for: ultrasound examination, audiometric and ophthalmoscope screening, as well as electroencephalography (EEG). Cerebral ultrasound is routinely performed at each visit; hearing and visual assessment is performed in all children at discharge and further is repeated in children who have had abnormal results at first examination. EEG examination is performed at indication of pediatric neurologist.

Specialized services are provided by specialists: neonatologist/pediatrician, neurologist, audiologist, ophthalmologist, radiologist, specialist in EEG, kinetotherapist, psychologist and speech therapist. Specialists from multidisciplinary team perform a comprehensive neurodevelopmental examination at discharge at 3, 6, 12, 18 and 24 months. For premature babies up to 34 weeks of gestation the neurodevelopmental assessment is made at corrected age (*Corrected age = Current age - (40 weeks - Gestational age)*.

Strengthening and regionalization stage. As the number of children requiring surveillance was increasing, there has appeared a need to open beside the Republican Follow-up Centre another 4 regional centers, which create now a regionalized service of follow-up. Regional centers only provide specialized Follow-up services for newborn population at risk from northern, central and southern geographical areas, as well as from the country's capital – Chisinau city. The first neurodevelopment evaluation of a baby only occurs at the Republican Center and if a severe risk for neurodevelopment is established the child continues to be monitored at this Center, and if the risk is found to be mild or minor the baby is referred to the Regional Center. Follow-up centers co-work with local primary care facilities which refer to the follow-up visits the children included in the follow up program and with rehabilitation institutions.

Stage of the Follow-up integration in the Early Intervention Service. The Regulation-framework and minimum standards of Early Intervention Services were elaborated recently and are currently being approved by the Government.

The Regulation on the organization and operation of the Early Intervention Service for Children has been elaborated based on the Law nr. 169 from 09.07.2010 within the Strategy of Social Integration of Persons with Disabilities (2010-2013).

The Early Intervention for Children (EIC) is a system of integrated, multidisciplinary services provided to the child starting with his birth up to 5 years of his life and to his family in case of developmental disorders or of an increased risk for its optimal development due to the influence of risk factors of biological nature or related to the environment before birth or during delivery.

The EIC system is based on effective partnership between professionals from medical, educational and social spheres together with family members, which is carried out through the activities in interdisciplinary teams.

The purpose of the Early Intervention for Children is the creation of optimal environment for harmonious development of a child aged 0-5 years with special needs, to promote his development (physical, intellectual, social and emotional), to improve family skills for ensuring care and development of the child, taking into account his specific features and age, to promote the idea of a partnership with the family through establishing the support for social integration of the child and family, including services on information and counseling.

Beside the diagnostic and neurodevelopmental follow-up, inclusively the audiometric and ophthalmoscope services, the Early Intervention Service for Children includes another services: on ensuring nutritional needs, psychological services for family and children, rehabilitative and nursing services, the social assistance services, services on stimulation and correction of communication, language and family support services.

After approval of the Law on early intervention services, the Follow-up service operation will strengthen and expand geographically, being parallel extended with the period for follow-up of children from risk groups up to 3 years. Parallel there will be developed early intervention services for the recovery of children with disabilities. The Government and international bodies, as well as bilateral donors, are supporting the training and certification process of the state institutions and NGOs for providing early intervention services.

Compartment 2. Neurodevelopmental outcomes of premature infants at 2 years corrected age depending on their birth weight.

The study's **goal** was to assess neurodevelopment, neurosensory functions (hearing and visual outcome) and growth at 2 years in premature infants born with birth weight less than 1500 g and more than 1500g.

Materials and methods. This retrospective descriptive study was conducted at the MCI from January 1, 2008 to December 31, 2010. The case notes of 155 babies with 6 follow-ups done, the last done at 24 months, were analyzed. Children were divided into 2 groups: group I 128 children with birth weight less then 1500g and group II - 27 children with birth weight more than 1500g.

Assessment. Neurodevelopmental follow-up started at 3 months postnatal age and ended at 2 years. Modality of effectuating developmental assessments is described above. Grading of neurodevelopmental impairment by domain (motor, vision, hearing, speech, cognition, behavior and seizures) was made according to guidelines provided by the International Classification of Functioning as mild, moderate, or severe if functions were >50%, 25% to 50%, or <25% of the gold standard, respectively. The severe disability was defined as mental retardation, cerebral palsy, epilepsy, blindness, and/or moderate to severe hearing impairment.

We used the Bayley Scales of Infant Development III (BSID-III) to evaluate cognitive functioning between 3 months and 2 years. Assessment of motor outcomes was performed at each follow-up visit with a formal neurologic exam. Severity of cognitive and motor impairments was graded according to the MDI and PDI scores, using the following cutoff points: a) >85 was considered as normal, b) 71 to 85 was considered as mild impairment and c) ≤70 was considered as severe impairment. This assessment was made according to the corrected age.

Results. There are statistically significant differences ($p<0.001$) between cases of antenatal use of glucocorticoids with a prophylaxis aim with a prevalence in group I in 50,78% of cases (65), compared to 11,11% (3) cases in group II, as well as of intrapartum prophylactic administration of antibiotics ($p<0.001$): 50,78% (65) in group I compared with 14,81% (4) cases in group II.

The study on pregnancy and birth complications showed no statistically significant differences in both groups.

In group I girls have prevailed (75 to 58,59%) than boys (53 to 41,4%), while in group II there was no difference between the number of girls (13 to 48,15%) at the boys (14 to 51,85%).

Most children 102 (65.5%) were born at level 3 being referred in utero. Gestational age of children was between 24 and 37 weeks in group I there were children with g.a. 24-26 weeks and 35-37 weeks, compared with no child of this age in group II (Table 1).

Table 1.

Gestational age of children enrolled in Follow-up study

G.a., weeks	Groups of children	
	I – with birth weigh <1500g, n=128	**II** – with birth weigh ≥1500g, n=27
35-37	2 (1,56%)	0
34-32	17 (13,28%)	9 (33,33%)
31-29	64 (50%)	13 (48,15%)
28-27	37 (28,9%)	5 (18,52)
24-26	8 (6,25%)* ($p<0.05$)	0
Total	128 (100%)	27 (100%)

*($p<0.05$) statistical difference between groups I and II

Analysis of morbidity at the moment of enrollment in the program (Table 2) showed a statistically significant prevalence of cases of intraventricular hemorrhage (IVH) of grade I and II, periventricular leukomalacia (PVL), convulsions, hypoglycemia, hyperbilirubinemia and retinopathy of prematurity (ROP) in infants from group I, compared with group II. We can observe a higher frequency of cases of early sepsis in neonates weighing less than 1500g and of late sepsis in neonates weighing more than 1500 g in both cases with no significant differences.

Table 2.

Morbidity at discharge in children enrolled in study

Nosology	Groups of children	
	I – with birth weight <1500g, n=128	**II –** with birth weight ≥1500g, n=27
Early sepsis	14 (10,94%)	1 (3,7%)
Late sepsis	7 (5,47%)	3 (11,11%)
Meningitis	3 (2,34%)	1 (3,7%)
Pneumonia	83 (64,84%)	20 (74,07%)
Necrotizing enterocolitis (NEC)	12 (9,37%)	2 (7,4%)
Respiratory distress syndrome (RDS), severe	11 (8,59%)	1 (3,7%)
RDS, moderate	36 (28,12%)	7 (25,92%)
RDS, mild	22 (17,19%)	2 (7,4%)
Intraventricular hemorrhage (IVH), grade I	20 (15,62%)*	1 (3,7%)
IVH, grade II	17 (13,28%)	1 (3,7%)
IVH, grade III	6 (4,68%)*	0
Periventricular leukomalacia (PVL)	6 (4,68%)*	0
Bronchopulmonary dysplasia (BPD)	3 (2,34%)	0
Convulsions	7 (5,47%)*	0
Hypoglycemia	22 (17,18%)***	0
Hyperbilirubinemia	27 (21,09%)***	0
Retinopathy of prematurity (ROP)	6 (4,68%)*	0

*($p<0.05$), ** ($p<0.01$) statistical difference between groups I and II

Evolution of the neurodevelopmental diagnoses at 12, 18 and 24 months is shown in table 3. Therefore, at 2 years 71 (66,36%) children from group I and 17 (73.91%) children from group II were diagnosed to be healthy. There is no statistically significant difference between the number of cases of mild and moderate neurological disorders at 24 months of corrected age between the compared groups. At 12 months corrected age the significant prevalence of moderate disorders in children weighing less than 1500 g birth is observed compared to those with birth weight more than 1500g ($p<0,05$). Although there is no statistically significant differences between the frequency of severe neurodevelopmental impairment between groups at evaluated ages, though their prevalence is obvious in children from group I (13,08% of total cases of cerebral palsy in 7,5% cases) compared to group II (4,34% of total cases being represented by cerebral palsy), followed by hydrocephalus/ ventriculomegaly etc. The same dynamics is observed also in the analysis of the vision disorders.

Different domains of composite score (cognitive, language, motor) assessed using Bayley score are shown in the table 4. Comparison of composite scores values, that were analyzed as a norm and impairment (mild and severe), highlights in babies with birth weight less than 1500g the prevalence of language impairment (18,96%) compared with motor (14,95%) and cognitive impairment (13,93%). Statistically significant differences between the values of composite score per functions were obtained only for the cognitive one ($p<0,05$) and language ($p<0,01$) in the direction of predominance of the mild impairment in children with birth weight less than 1500g compared to children with birth weight more than 1500g. Children from group II have had similar disorders on average in 5% of cases for each of the functions described. On the other hand many children with birth weight more than 1500g at 2 years corrected age had a normal development of cognitive (95,83%), language (95.24% and motor functions (95.65%).

Table 3

Diagnosed neurological disorders in premature infants weighing up to 1500 g and more than 1500g in the Follow-up framework at 12, 18 and 24 months corrected age

Neurological disorders	12 months		18 months		24 months	
	Groups of children					
	I – with birth weight <1500g, n=122	**II** – with birth weight ≥1500g, n=27	**I** – with birth weight <1500g, n=116	**II** – with birth weight ≥1500g, n=21	**I** – with birth weight <1500g, n=107	**II** – with birth weight ≥1500g, n=23
Healthy	63 (51,65%)	19 (70,37%)	77 (66,38%)	19 (90,47%)	71 (66,36%)	17 (73,91%)
Mild cerebral disorders	7 (5,74%)	1 (3,7%)	9 (7,76%)	3 (14,28%)	14 (13,08%)	5 (21,74%)
Moderate disorders	25** (20,49%)	1 (3,7%)	5 (4,31%)	0	1 (0,93%)	0
Severe disorders	14 (11,47%)	2 (7,4%)	12 (10,34%)	1 (4,76%)	14 (13,08%)	1 (4,34%)
- Cerebral palsy	7 (5,74%)	1 (3,7%)	7 (6,03%)	1 (4,76%)	10 (9,35%)	1 (4,35%)
- Hydrocephaly/ ventriculomegaly	4 (3,28%)	1 (3,7%)	3 (2,58%)	0	2 (1,87%)	0
- Microcephaly	3 (2,45%)	0	2 (1,72%)		2 (1,87%)	0
ROP	2 (1,64%)	0		0	0	0
Partial atrophy of n. opticus	1 (0,82%)	0	1 (0,86%)	0	2 (1,87%)	0

** ($p<0.01$) statistical difference between groups I and II

Table 4.

Cognitive, motor and language functions assessed at 2 years corrected age

Composite score		Functions / Groups of children					
		Cognitive		Language		Motor	
Score	**Interpretation**	**I** – with birth weight <1500g, n=122	**II** – with birth weight ≥1500g, n=24	**I** – with birth weight <1500g, n=116	**II** – with birth weight ≥1500g, n=21	**I** – with birth weight <1500g, n=107	**II** – with birth weight ≥1500g, n=23
>85	Norm	105 (86,1%)	23 (95,83%)	94 (81,03%)	20 (95,24%)	91 (85,05%)	22 (95,65%)
71-85	Mild impairment	7 (5,74%)*	0	11 (9,48%)**	0	3 (2,80%)	0
≤70	Severe impairment	10 (8,19%)	1 (4,17%)	11 (9,48%)	1 (4,76%)	13 (12,15%)	1 (4,34%)

*($p<0.05$),**($p<0.01$) statistical difference between groups I and II

We have determined in both groups that along with the increase of the number of functions affected at the use of BSID-III the severity of neurodevelopmental disability also is in increase. Thus, at damage of a single function or in some cases two functions, children have had moderate impairment, and at damage of all three functions - severe neurodevelopmental impairment.

Besides neurological pathology, premature babies have suffered from other morbidities (table 5). Thus, at corrected age 24 months a third part of children with birth weight under 1500g were somatically healthy, compared to approximately fifty percent of children weighing more than 1500g. Among the complications of prematurity anemia, acquired malnutrition and respiratory diseases prevailed. Respiratory pathology increases along the children growth probably due to the fact that children are more in a contact with the surrounding world. By 24 months the incidence of anemia in children weighing less than 1500g is decreasing in both groups with a higher percentage of children weighting more than 1500g, which can be explained by the low number of cases in this group and possibly by a greater attention focused on anemia prevention in children weighing less than 1500g.

Discussions. The Follow-up study's data represent the first results of the implementation of this technology in the country compared with the 20-30 years experience in this service existing in developed countries.

Although gestational age is a stronger determinant of biological maturation than a birth weight, though it allows detecting SGA children [9], the selection of the method of grouping the outcomes of our study was done by taking the birth weight as basis. A small number of cases in some categories of gestational age can serve as explanation of this fact.

Table 5

Post discharge morbidities diagnosed in children enrolled in Follow-up at 12, 18 and 24 months corrected age

Post discharge morbidities	12 months		18 months		24 months	
	Groups of children					
	I – with birth weight <1500g, n=128	**II** – with birth weight ≥1500g, n=27	**I** – with birth weight <1500g, n=128	**II** – with birth weight ≥1500g, n=27	**I** – with birth weight <1500g, n=128	**II** – with birth weight ≥1500g, n=27
Healthy	6 (4,68%)	10 (37,04%)	40 (31,25%)	13 (48,14%)	40 (31,25%)	13 (48,14%)
Anemia	50 (39,06%)	9 (33,33%)	28 (21,87%)	10 (37,04%)	21 (16,41%)	7 (25,93%)
Respiratory morbidities	21 (16,41%)*	1 (3,70%)	11 (8,59%)	2 (7,41%)	16 (12,50%)	4 (14,81%)
Allergic diathesis	6 (4,68%)*	0	9 (7,03%)	3 (11,11%)	11 (8,59%)	1 (3,70%)
Rachitis	6 (4,68%)*	0	0	0	0	0
Coxofemoral dysplasia	2 (1,56%)	0	1 (0,78%)	0	0	0
BPD	1 (0,78%)	0	1 (0,78%)	0	0	0
Congenital hypothyroidism	3 (2,34%)	0	0	0	0	0
Streptodermia	1 (0,78%)	0	0	0	0	0
Acquired malnutrition	27 (21,09%)	3 (11,11%)	25 (19,53%)*	1 (3,70%)	18 (14,06%)	5 (18,52%)

*($p<0.05$) statistical difference between groups I and II

Taking into account that out of 155 children examined in the study only 8 (6,25%) were of g.a. 24-26 weeks, the outcomes of these children didn't strongly influence neurodevelopment outcomes in the entire group. Also because of the low proportion of premature newborns have completed all visits within 2 years, the results can also be interpreted as rather good in the entire group.

Total 15 (9,67%) of children showed severe neurological abnormality with a prevalence in the group with VLBW 14 (13,08%) due to cerebral palsy (CP) 10 (9,35%).

Thanks to advanced neonatal care and better facilities, the frequency of CP in VLBW and ELBW infants has reduced from 13% to 5% in western countries [12]. In specialized literature the rates of CP in ELBW vary from 50% to 30%, but are most commonly situated at 15% to 23% [1, 8]. In our study there were registered total 11 (7,09%) cases of CP (10 (9,35%) in group I and 1 (4,35%) in group II) which is explained by the fact that 24 (18,75%) children in group I had ELBW and 8 (6,25%) were of gestational age 24-26 weeks, which shows that the highest risk of PC takes place among tiny premature infants. Besides gestational age other additional specific perinatal risk factors for CP include neonatal sepsis (21 (16,41%) cases in group I and 4 (14,81%) cases in group II in our study) and NEC – 9,37% (12) cases in group I. A negative role belonged to the association of sepsis with meningitis (3 (2,34%) cases in group I and 1 (3,7%) case in group II) and other severe illness in newborn period (43 (33,6%) children in group I in our study had IVH of whom 6 (4,68%) IVH grade III ($p<0,05$), in comparison with only 2 (7,4%) babies in group II of I and II grade of IVH. Along IVH 6 (4,68%), $p<0,05$ children with VLBW have suffered from PVL, compared with no cases in group II. Three children from group I at 2 years were diagnosed to having post-hemorrhagic hydrocephalus and microcephaly.

Per total 88 (56,77%) children born prematurely at the age of 2 years were diagnosed as healthy, of them 71 (66,36%) children up to 1500 g and 17 (73,91%) children weighing more than 1500g the fact which supports the affirmation that most preterm infants have good neurodevelopmental outcomes. Every second child from group I has manifested neurodevelopmental impairment during psychological assessment using Bayley compared with only one child (□5%) in group II, shown mainly through the language ($p<0.05$) and cognitive ($p<0.01$) impairment. Average MDI score for babies with VLBW was 88,1, and for babies with bigger weight (≥1500g) it was 91,8 and is higher than that reported by NICHD at 18 to 22 months corrected age 76 with variations 70 to 83. [13]

All children from the study were screened for early signs of ROP by ophthalmologist at each visit until the 32 weeks corrected age. 45 (35,1%) of 128 children from group I and 5 (18,52%) children from group II had gestational age up to 28 weeks and presented a high-risk group for developing ROP than more mature children. Lack of aggressive therapies with O2 has influenced the small number of cases of ROP and lack of cases of BDP.

The existence of the database in the Republican Follow-up Centre which allows collecting data at the national population-based level is important because it can validly provide data in the future, and the incidence of outcomes will be more accurate. The study can be deepen by testing the influence of some interventions used during neonatal period on neurodevelopment and somatic health of premature children enrolled in the Follow-up Program.

There is evidence that early high quality parent-infant interactions have a positive influence on cognitive and social development in children [14]. There are several types of interventions such as physical therapy and infant stimulation programs that focus on infant development. Studies on the early interventions and rehabilitation testing are also possible in the future.

Another possible direction for the future research is the assessment of satisfaction of premature infants' mothers/parents with the Follow-up and Early Intervention services. Such studies have been made in some countries and have shown the ways that may improve these services.

Conclusions

1. Severity of neurodevelopmental impairment at 2 years corrected age was more advanced in children with VLBW (group I) due to a more complicated evolution of early neonatal period due to infectious complications (sepsis, meningitis, NEC), respiratory (RDS) and cerebral (IVH, p <0,05, PVL, p <0,05 and seizures, p <0,05) associated with prematurity.
2. Severe neurological disorders prevailed also in the group of children with VLBW in 13,08% (14) cases being represented in 9,35% of cerebral palsy, hydrocephaly / ventriculomegaly and microcephaly both per 1, 87% of cases.
3. Among the areas of neurodevelopment in VLBW babies, the cognitive ($p<0.05$) and language ($p<0.01$) functions have suffered more pronounced being manifested by the mild impairment.

References

1. Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. Pediatrics 2007; 119(1):37–45.

2. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196(2):147, e141–8.

3. Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. Semin Perinatol 2003;27(4):281–7.

4. Wilson-Costello D, Friedman H, Minich N, et al. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005;115(4):997–1003.

5. Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990s. Semin Neonatol 2000;5(2):89–106.

6. Bonnie E. Stephens, Betty R. Vohr. Neurodevelopmental Outcome of the Premature Infant. Pediatr Clin N Am 56 (2009) 631–646.

7. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002;288:728-37

8. Wilson-Costello D, Friedman H, Minich N, et al. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005;115(4):997–1003.

9. Als H. Program Guide - Newborn Individualized Developmental Care and Assessment Program (NIDCAP®): An education and training program for health care professionals. Rev ed. Boston, Mass: Children's Medical Center Corporation; 2002.

10. Jacobs S, Sokol J, Ohlsson A. The newborn individualized developmental care and assessment program is not supported by meta-analyses of the data. Journal of Pediatrics 2002;141(3):451-452.

11. Wood NS, Marlow N, Costeloe K, et al. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med 2000;343(6): 378–84.

12. Hack M., Taylor G., Droter D., Schluchter M., Cartar L., Andreias L. et al. Chronic Conditions, Functional limitations, and special health care needs of school aged children born with extremely low birth weight in the 1990's. JAMA 2005; 294:318-25.

13. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. Pediatrics 2000;105(6):1216–26.

14. Melnyk BM, Alper-Gillis, Fischbeck-Feinstein N. Improving cognitive development of low birth weight premature infants with the COPE program: a pilot study of the benefit of early intervention with mothers. Research in Nursing and Health 2001; 24:373-89