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Therapeutic diet using a special-purpose baby milk product for enteral nutrition with high content of protein and energy for children of the first year of life with protein-energy deficiency

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Children born prematurely, with extreme and very low birth weight, combined with severe perinatal pathology often have reduced growth rates during the first year of life and need special nutritional support. ***Research objective:*** *to study the physical development of infants with protein-energy deficiency using a special-purpose baby milk product for enteral nutrition with high content of protein and energy.* ***Methods:*** *the tolerability and effectiveness of therapeutic diet was studied in a prospective two-month observation in a series of cases. The actual nutrition and the chemical composition of children diets were assessed. The mass and body length, body mass index (BMI), the thickness of the skin-fat fold above the triceps were determined. The anabolic effect of therapeutic diet was assessed by the dynamics of the content of transthyretin.* ***Results:*** *the research included 30 infants with protein-energy deficiency, who were born full-term (n = 7) and preterm (n = 23), all with severe perinatal pathology. The good tolerability of the studied formula was fixed in most of the patients. Relief of functional disorders of the gastrointestinal tract (regurgitation, colic, meteriorism, constipation) was noted in 23 (87%) patients. Using the formula with high content of protein and energy in the therapeutic diet allowed meeting the needs of children in protein and improve their weight and growth parameters in most cases: BMI increased in 19 (72%), weight — in 16 (63%), body length —24 (92%), the thickness of the skin-fat fold above the triceps — in all (100%) children. Increase of transthyretin with concentration from 162 (157; 171) at the beginning of the research to 187 (170; 208) mg/l at its end (p = 0,028) is registered.* ***Conclusion****: a special-purpose product with high protein and energy for enteral nutrition can be used in the diet of infants with protein-energy deficiency who were born with severe perinatal pathology, including infants, who were born prematurely.*

Keywords: *infants, premature babies, hypotrophy, protein-energy deficiency, extreme low birth weight, very low birth weight, therapeutic diet.*

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RATIONALE

Premature babies born with severe perinatal pathology often have protein-energy deficiency and need special nutritional support. Whereupon, children born with very low (VLBW) and extremely low (ELBW) birth weight, intrauterine growth retardation often lag significantly behind in the physical and psychomotor development, impaired nutritional status in the form of malnutrition, not only during the first year, but later in life as well. [1] In particular, it was discover that among children born with VLBW and ELBW and treated in the department of regenerative treatment for infants with perinatal pathology in the Scientific Center of Children Health (Moscow) in 2010-2011, about 30% were suffering from varying degrees of protein-energy deficiency during the first year of life [2]. Normal growth and development of these children made considerable difficulties because of long-continued morphofunctional immaturity of organs and systems, which was a barrier to optimal nutrient absorption. Children had a reduced appetite, were able to assimilate only small amount of food, i.e. a vicious circle was being formed: there was an increased need for nutrients and energy, but the ability to assimilate them was limited.

It is now recognized that optimal physical development of child on with rationally organized nutrition in the first year of life is a health basis for all subsequent human life [3-5].

Nutritional support in the form of using a special-purpose product with increased content of protein and energy can stimulate anabolism and lead to the target levels in nutrition, which, in turn, will stimulate physical and psychomotor development of a child [6]. However, the dependence of growth rates, protein metabolism on nutrition types, nutrients ratios and energy value has not been properly researched yet in infants with severe perinatal pathology, since the first days of life. In the earlier research, it was shown that such indicators of protein metabolism as total protein, urea, and transthyretin are lower in immature premature children receiving breast milk, compared to children, who were fed with mixture for preterm infants. This demonstrates the need of nutrition optimization with an increase in the protein quotas [7].

Several studies show that protein and energy deficiency during critical periods of prematurely child development leads to adverse remote effects in form of persistent delays in physical development, cognitive disorders and behavioral responses [8, 9]. According to F. de Zegher et al., there is a close relationship between intrauterine growth retardation, carbohydrate metabolism, child growth and the nutrition at an early age [10].

In the Russian Federation the term "hypotrophy", which defines body mass deficits relative to body length, child's age, has traditionally been used for the diagnosis of child nutrition. According to the on-stream classification by E.V. Neudahin (2001), there is a pre- and postnatal forms of hypotrophy, which, in turn, divide weight deficit by degree in the following way: I (10-20%), II (20-30%), III (30% and higher) [11]. There may be various causes of hypotrophy. These may include diseases of perinatal period: chronic intrauterine fetal hypoxia, prematurity, intrauterine infections, perinatal brain damage, developmental abnormalities, etc. If there is a long-term current chronic nutrition disorder, metabolic disturbance is gradually increasing: protein catabolism begins to prevail over its synthesis, fat and carbohydrates reserves are depleted, macro- and microelements deficiency is received. Consequently, immune function suffer, brain growth and development are violated. [12] As a result, these children often fall behind their peers in psychomotor development [12, 13].

According to the International Classification of Diseases, 10th Edition, chronic nutrition disorders in infants, developing/continuing postnatally, are regarded as protein-energy deficiency (E43, E44). The reasons for such violations may be inadequate intake of food (anorexia, vomiting, and others), increased losses during severe diseases (hypermetabolism), hypercatabolism and others. Often the causes of protein-energy deficiency in children with severe perinatal pathologies are concomitant [12, 13].

The aim of our research was to investigate physical development of infants with protein-energy deficiency using a special-purpose baby milk product for enteral nutrition with high content of protein and energy.

METHODS

RESEARCH DESIGN

A prospective research with analysis of a series of cases was carried out.

ELIGIBILITY CRITERIA

Criteria for inclusion of children in the research:

- age ≥1 month;
- weight ≤8000 g;
- protein-energy deficiency that developed antenatally (premature infants with intrauterine growth retardation);
- postnatal protein-energy deficiency;
- the absence of pronounced symptoms of functional disorders of the gastrointestinal tract, GIT (abundant regurgitation, colic, loose stool, constipation);
- mixed and artificial feeding.

Criteria for exclusion of children from the research:

- acute infectious diseases;
- the child's refusal to receive the product;
- the emergence of food allergy symptoms;
- the emergence or increased violations of GIT (regurgitation, colic, loose stool, constipation).

The criterion of protein-energy deficiency was body mass index (BMI) below the 10th percentile (for both full-term and preterm infants) for the respective age groups.

CONDITIONS

The research was conducted at the Scientific Center of Children Health (Moscow) based on the department of regenerative treatment of children with perinatal pathology.

DURATION OF THE RESEARCH

The inclusion period lasted 4 months, from January to July 2013. The observation period was 2 months followed by the control of the parameters investigated after 1 and 2 months.

THERAPEUTIC DIET

All the children included in the research, received a nutritionist consultation, where their diets were corrected in accordance with the "National nutrition optimization program for children of first year of life in the Russian Federation" [5, 14, 15]. All the children were assigned to therapeutic diet "Infatrini"/INFATRINI (Nutricia Advanced Medical Nutrition, the Netherlands), with the amount determined individually, depending on the age and nutritional status of the child. The mixture was recommended to be used both independently and by diluting dairy-free cereal. The product was administered in the diet by the scheme, starting from 5-10 ml/day, further increasing gradually to 200ml during 7-10 days. The maximum amount of therapeutic mixture in the course of the research was 300 ml/day.

THE STUDY OF THE DIET

Daily consumption of major nutrients and energy by children was evaluated at the time of including the children in the research, and after correcting the nutrition. The calculation was based on data about the daily amount of consumed breast milk/milk mixture and supplemental feeding and the content of energy and macronutrients that were studied [16]. The results received were interpreted in accordance with accepted standards in the Russian Federation for the physiological need of children of the first year of life [17] and the estimated need for nutrients and energy for infants born preterm (table. 1) [5, 18]. The diet was considered unbalanced if any indicator deviated by 10% in either

direction from the regulatory values.

Table 1. Average daily rate of physiological needs for nutrients and energy for children of the first year of life (per 1 kg of body weight)

Age groups	Proteins, g	Fat, g	Carbohydrates, g	Energy, kcal
Born at full term children				
1–3 month	2,2	6,5	13	115
4–6 month	2,6	6,0	13	115
7–12 month	2,9	5,5	13	110
Premature babies				
1–3 month	2,5–3,0	6,5	14	120–130
3–6 month	2,9–3,2	6,6–7,0	14	120–130
7–12 month	3,2	6,0	14	115–120

THE OUTCOME OF THE RESEARCH AND ITS ASSESSMENT

The following indicators of physical development of the children were measured every month during the observation period:

- body weight using standardized scales;
- body length with the use of a stadiometer;
- thickness skin-fat fold above the triceps using a caliper.

Tolerability of the product was monitored daily: the kind of appetite, new or worsening regurgitation, meteorism, changes in stool frequency and consistency. Besides, skin condition was also assessed.
In order to determine the adequacy of nutritional support, the direction of anabolic/catabolic processes there was carried out an assessment of serum transthyretin content at the start and at the end of the research (in CCDL SCCH by enzyme immunoassay analysis method on a biochemical analyzer Beckman Coulter UniCel DxC 600, USA). Transthyretin is a sensitive indicator of protein synthetic liver function with a short (1-2 days) half-life. Its low (reference values - 180-380 mg/l) content in blood serum can serve as a indicator of protein-energy deficiency.

ETHICAL EXPERTISE

The research was conducted in accordance with GOST R 52379-2005 "Appropriate Clinical Practice" [19]. Parents of all children had provided informed consent for the research.

STATISTICAL ANALYSIS

The selection size has not been not calculated preliminarily. Statistical analysis was performed using STATISTICA software package v. 6.0 (StatSoft Inc., USA). Quantitative data were presented in a form of median (25th, 75th percentiles). Wilcoxon test was used for comparing dependent. Differences were stated as statistically significant at $p < 0,05$.

RESULTS

THE PARTICIPANTS OF THE RESEARCH

The research involved 30 children (including 20 girls) of the first year of life with protein-energy deficiency. Gestational age at birth ranged from 25 to 40 weeks. There were 24 children born prematurely, among them 12 with ELBW (<1000 g), 9 with VLBW (1001-1500 g), 3 with low birth weight (LBW, 1001-1500 g). 6 children were born full-term (birth weight> 2500 g). The data on body weight, body length, head and breast circumference at birth of the children included in the research are presented in the table 2. Intrauterine growth retardation was reported in 10 patients. At the start of the research, the actual age of the children ranged the normal gestational weeks from 12 to 65 weeks, corrected age (the actual age minus the number of missing to normal duration of pregnancy) — from 4 to 56 weeks.

Table 2. Anthropometric data of children with different birth weight

Birth weight, g	Body weight, g	Body length, sm	Head circumference, sm	Breast circumference, sm
<1000	843 (727; 925)	34 (30,5; 36,5)	24,5 (23; 25,5)	21 (20; 22)
1001–1500	1270 (1220; 1350)	38,5 (37; 40,5)	29 (24; 30)	25 (23,5; 25,5)
1501–1200	1990 (1970; 2000)	43 (43; 44)	31 (31; 31)	27 (27; 27)
>2500	3490 (2880; 3850)	51 (48; 52)	34 (32; 35)	32 (28; 32)

All children had psychomotor retardation, muscular dystonia syndrome due to perinatal lesions of the central nervous system of heavy and medium severity. Bronchopulmonary dysplasia was diagnosed mainly in the children born with ELBW and VLBW (n = 11). Among the children born with VLBW, the following diseases were diagnosed 1 case each: congenital heart disease, polycystic kidney disease, Silver-Russell syndrome; among children with NTM — hydrocephalus; among the children born with normal body weight — 1 case of spinal amyotrophy Wernig-Hoffmann, velocardiofacial syndrome, Costello syndrome, Robinov syndrome. The severity of the main disease is regarded as heavy in 26 (87%), medium — in 4 (13%) children. Skin and visible mucous membranes, at the start of the research, were clean at all (100%) children.

Actual nutrition analysis showed that 3 (10%) of the child received breast milk, special-purpose infant mixtures for premature infants after discharge was given to 2 (7%) patients. The rest of the children received supplemental feeding with a variety of adapted milk mixture. 3 (10%) also received mixture based on protein hydrolysate, 3 (10%) — mixture for premature babies, 2 (7%) children — hypoallergenic.

The analysis of the diet of the children, conducted at the start of the research, showed that all the observed children, born with heavy perinatal pathology, including with VLBW and ELBW, had unbalanced diet in terms of macronutrients and energy content (norms of physiological needs are presented in table 1). Insufficient amount (per 1 kg of body weight) of protein was obtained by 18 (60%), excessive — by 9 (30%); insufficient fat — by 22 (73%), excessive — by 4 (13%); insufficient amounts of carbohydrates — by 18 (60%), excessive — by 7 (23%) children. Caloric deficit was fixed in 18 (60%), the excess — in 8 (27%) patients (fig.). In 8 (67%) of children born with ELBW, there was an excessive intake of protein, in 6 (50%) of them had increased caloric intake. Among the children born with VLBW, 8 (89%) patients were reported to have insufficient intake of protein and energy.

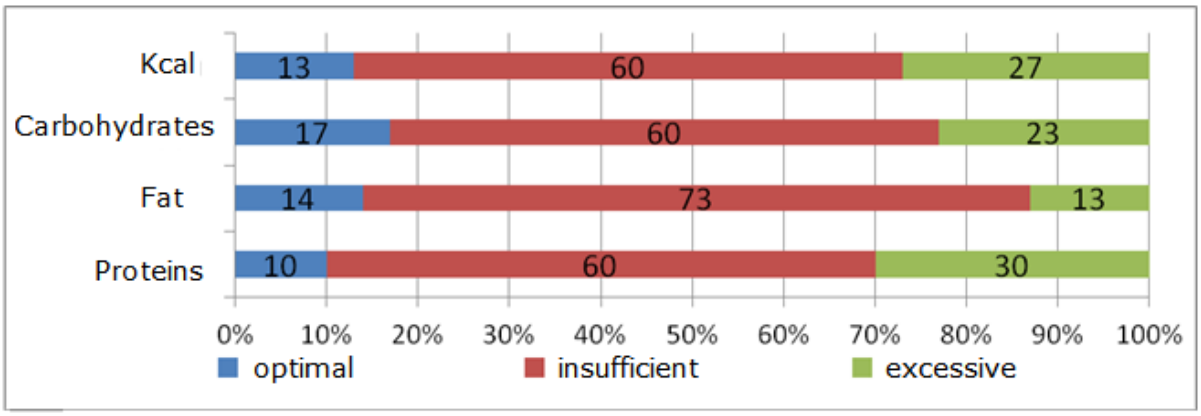

Fig. Consumption of nutrients and energy by children at the start of the research

TOLERABILITY AND EFFECTIVENESS OF THE THERAPEUTIC DIET

The period of adaptation to a special-purpose children milk product for enteral nutrition with high content of protein and energy in 26 (87%) children proceeded without peculiarities. Children ate the mixture willingly, there was no failure in its receiving.

Symptoms of gastrointestinal dysfunction at the start of the research had the following frequency: regurgitation syndrome and bloating — in 1, colic — in 6, constipation — in 10 children. In the

course of the research the symptoms listed above were stopped in all (100%) the children. New cases of gastrointestinal dysfunction were not reported.
The results of the research showed that a sufficient increase (values of physical development after 2 months were within 25-75th percentiles of the age norm) in body length was registered in 23 (92%); in body weight — 19 (63%); thickness skin-fat fold above the triceps — in all (100%); BMI — in 18 (72%) children (table 3). In addition, an increased concentration of transthyretin was registered in 21 of 26 (81%) children.

Table 3. The dynamics of physical development indicators in children receiving therapeutic diet

Indicator	**In the start**	**After 1 month**	**After 2 months**	***p***
Age, weeks	28 (20; 32)	32 (24; 36)	36 (28; 40)	–
Body weight, g	5915 (5245; 6500)*	6170 (5609; 6824)	6590 (6000; 7100)*	0,001
Body length, sm	64 (61; 69)*	65,5 (63,5; 68,5)	68 (65; 69,5)*	0,001
SCF, mm	7,0 (5,5; 8,0)*	8,0 (7,0; 9,0)	9,0 (8,5; 10,0)*	0,001
BMI, kg/m2	14,1 (13,4; 14,8)*	–	14,6 (13,8; 15,0)*	0,049
Transthyretin, mg/l	162 (157; 171)*	–	187 (170; 208)*	0,028

Note. SCF — subcutaneous fat, BMI — body mass index. * — the indicators, measured in the start and after 2 months, are compared

UNWANTED OCCURANCES

At 1(3%) child on the 16th day of the research there was regurgitation after each feeding stated. For this reason, the special-purpose children milk product was canceled. In 3 (10%) of premature infants on the 2nd-3rd days after the administration of the product appeared symptoms of skin allergy: in 1 child — hyperemia and peeling in the cheek area, in 1 — papular rash allergies in the chest area, in 1 — common allergic rash. Allergic history was burdened in 1 case. These children were excluded from the research.

DISCUSSION

It is known, that a high-energy milk mixture is generally well tolerated in children with poor weight gain [20, 21]. This observation is consistent with the results of this research: amid the complex therapy, including the gradual introduction of therapeutical diet, such symptoms of gastrointestinal dysfunction as regurgitation, flatulence, colic was stopped in almost all the patients.

A research, conducted at the Medical Center of the University of Maastricht (the Netherlands), reported that early use of high-protein mixture with a high caloric value in heavily ill children with respiratory failure due to the RS-viral bronchiolitis provides adequate intake of nutrients and improves energy and nitrogen balance without side effects [20].

In an open randomized research in children with poor weight gain, the effectiveness and safety of the mixture with an increased content of nutrients and the mixture with an increase in calories were compared. It is shown that the concentration of urea in blood of the children, treated with a mixture with increased calorie throughout the research period, decreased by 50%, that indicates the protein and energy suboptimal ratio in the mixture. While using the mixture with increased content of nutrients normal average concentration of urea in the blood retained, also no significant reduction of z-height to age indicator was observed in the control group. It is concluded, that the increase in energy content of conventional nutrient mixtures for children without increasing the content of protein and micronutrients, should not be used for children with poor weight gain [22].

Our work shows that in most cases the diets of children with protein-energy deficiency does not satisfy their needs for main nutrients and energy. Despite the efforts of some doctors to improve the nutritional and energy value of the diet, the imbalance on the main nutrients and energy is still observed, and this ultimately leads away from the desired result — adequate growth and development of the child. Children who are able to digest only limited amount of nutrition, require strictly

individualized approach in formulating their diet, with the use of special-purpose high-protein high-calorie products for enteral nutrition.

A good anabolic effect of therapeutical diet with increased content of nutrients and energy is illustrated in the results of double-blind randomized controlled research. Increasing of protein and calories intake stimulates protein anabolism in heavily ill children during the first days after the prescription. The analysis showed that synthesis and protein balance indicators in the body were significantly higher in the group treated with the mixture rich in proteins with increased calorie, in comparison with the group, which used the standard mixture. Thus, in the group treated with the mixture rich in proteins with increased calorie, protein positive balance was achieved, which was significantly higher than the corresponding values in the group receiving a standard mixture [23]. These data are consistent with the results of our research which reported the following: during 2-month high-calorie high-protein therapeutical diet the majority (78%) of children had increased amount of serum transthyretin protein content. This shows the adequacy and sufficiency of protein-energy nutrition for children participating in the research.

CONCLUSION

Special-purpose high-protein high-calorie product for enteral feeding is well tolerated in infants with protein-energy deficiency. Its use as a part of a therapeutical diet allows meeting the needs of these children in protein, energy and improving their weight and growth performance. The increase of transthyretin content observer in most children indicates the effectiveness of nutritional support of this ongoing therapeutical diet. Insignificant effect of using the mixture in some of the children was apparently caused by heavy perinatal and syndromic pathology in them. Possibly, in order to get more significant positive effect in these children the duration of the product intake needs to be prolonged. Special-purpose high-protein high-calorie product for enteral feeding can be used in the diet of term, preterm children born with intrauterine growth retardation, perinatal pathology and postnatally developed protein-energy deficiency. Children who are able to digest limited amount of food, require strictly individualized approach when formulating the diet.

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Conflict of interests

T.V. Turti — reception of a research grant from PLC «PROGRESS».

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