

Marta Białecka-Pikul[1], Ryszard Lauterbach[2], Dorota Pawlik[2]

MAY THE SUPPLEMENTATION OF LIPID EMULSION CONTAINING DHA IN VLBW INFANTS INFLUENCE THEIR PSYCHOLOGICAL DEVELOPMENT EVALUATED AT THREE YEARS OF AGE? PRELIMINARY STUDY

CZY PODAŻ EMULSJI TŁUSZCZOWEJ ZAWIERAJĄCEJ DHA U NOWORODKÓW Z BARDZO MAŁĄ MASĄ URODZENIOWĄ CIAŁA MOŻE WPŁYWAĆ NA ICH ROZWÓJ PSYCHICZNY OCENIANY W WIEKU TRZECH LAT? DONIESIENIE WSTĘPNE

[1]Institute of Psychology, Jagiellonian University, Cracow, Poland
[2]Department of Neonatology Collegium Medicum, Jagiellonian Univeristy, Cracow, Poland

Abstract

Objectives: *The aim of the study was to evaluate the possible influence of a lipid emulsion containing DHA (docosahexaenoic polyunsaturated fatty acid), parenterally administered from the first day of life, on the psychological development of 3-year-old children born with very low birth weight (VLBW). It was suspected that an increased amount of DHA in parenteral nutrition may be a variable that modifies the relation between other medical or social factors and their influence on the child's development.*

Material and methods: *Two groups of three-year-old children with calendar age ranging from 29 to 51 months (mean value – 38 months) were tested. The children in the study group (n=23) were parenterally nourished during the first weeks of life with a lipid emulsion containing DHA. The patients in the control group (n=13) were fed with a lipid emulsion without DHA.*

Results: *Using the General Linear Model (GLM) with the analysis of interaction effects, it was found that the supplementation of the lipid emulsion containing DHA in parenteral nutrition from the first day of life beneficially influenced the relation between immaturity associated with the children's health status at birth and emotional development evaluated at three years of age. It also modified the relation between emotional and linguistic development.*

Conclusions: *When administered after birth in prematurely born children, the lipid emulsion containing DHA may influence their development at the age of three years. It may either compensate the negative effects that immaturity associated with the health status at birth has on emotional development, or stimulate the language development in children whose emotional development is normal.*

Key words: parenteral nourishment, docosahexaenoic acid, VLBW newborns, psychological development

Streszczenie

Cel pracy: *Celem badań było sprawdzenie, czy podawana pozajelitowo w pierwszych dniach życia tłuszczowa emulsja zawierająca kwas dokozaheksaenowy (DHA) może wpływać na rozwój psychiczny trzyletnich dzieci, które urodziły się z bardzo małą masą urodzeniową (VLBW). Opisano odległe działanie DHA na rozwój, zakładając, że ten kwas tłuszczowy stanowi zmienną latentną, która modyfikuje związki zachodzące między innymi czynnikami społecznymi i medycznymi, mającymi wpływ na rozwój dziecka.*

Materiał i metody: *Oceniano dwie grupy dzieci w wieku trzech lat, urodzonych jako noworodki z bardzo małą urodzeniowa masą ciała (średnia wieku =38 miesięcy, zakres od 29 do 51 miesięcy). Grupę badaną stanowiło 23 pacjentów, którym w pierwszych tygodniach życia pozajelitowo podawano tłuszczową emulsję zawierającą DHA. Grupa kontrolna liczyła 13 dzieci, u których stosowano również emulsję tłuszczową, ale bez zawartości DHA.*

Wyniki: *Stosując Ogólny Model Liniowy (GLM) wraz z analizą interakcji stwierdzono, że podaż emulsji tłuszczowej zawierającej DHA w żywieniu parenteralnym u noworodków z bardzo małą masą urodzeniową wpływa korzystnie na relację między stanem zdrowia wynikającym z niedojrzałości nowo--rodka a rozwojem emocjonalnym ocenianym w wieku trzech lat oraz, że modyfikuje ona również relację między rozwojem emocjonalnym a językowym.*

Wnioski: *Podaż emulsji tłuszczowej zawierającej DHA w żywieniu parenteralnym u noworodków urodzonych przedwcześnie z bardzo małą masą urodzeniową ciała może u tych dzieci kompensować negatywny wpływ niedojrzałości wyrażający się w złym stanie zdrowia po narodzinach na rozwój emocjonalny oceniany w trzecim roku życia. Może także stymulować rozwój językowy u tych dzieci, które wykazują prawidłowy rozwój emocjonalny w trzecim roku życia.*

Słowa kluczowe: odżywianie pozajelitowe, kwas dokozaheksaenowy, noworodki z bardzo małą masą urodzeniową, rozwój psychiczny

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INTRODUCTION

Current studies evaluating the effects of preterm birth on child development are mostly longitudinal (1-5). These investigations have examined the medical and social risk factors causing disabilities and illnesses, as well as factors that may protect children from disturbed development. According to the dynamic systems theory, the child's psychological development is a dynamic process in which new structures and functions emerge through a system of internal feedback, involving processes of reciprocal interaction between the child and his/her environment (6). These systems are mutually embedded and hierarchical, so that the investigation of only one of them (e.g. somatic factors), does not necessarily explain or predict the children's developmental changes. Moreover, the importance of each developmental factor such as immaturity associated with health status at birth, the presence of parental care, or nourishment should be considered in relation to each other and it should also be remembered that they can have either a direct and immediate or indirect and distant, or even a latent effect on the developmental status of a child.

Nourishment during early life stages seems to be one of the crucial factors in development. Preterm infants have a significantly shorter time to obtain different vital substances across the placenta from the mother. One example of such compounds is docosahexaenoic fatty acid, DHA, which is an important factor in brain and retinal development (7-10). In the last 17 weeks of gestation, the brain of the fetus increases its volume five to six - fold, which is more than it increases at any other time in life. Premature birth disrupts the active accretion of DHA by the fetus. Moreover, lipid parenteral emulsions available for nourishment in the first few weeks after birth, usually do not contain DHA. Feeding preterm infants with emulsions containing DHA from the first day of life has been found to reduce severe stages of retinopathy of prematurity and cholestasis (11). It seemed important to assess the influence of such modified nourishment on the psychological development of children who were born prematurely. It is known that DHA is a polyunsaturated, fatty omega-3 acid, which is present in high concentration in the central nervous system and can serve as a latent resource that may have a direct or indirect effect on psychological development.

The primary purpose of the present study was to evaluate the effect of the parenteral administration of a lipid emulsion containing DHA on the neurodevelopment of very low birth weight infants in the context of the domestic environment during early life. The results of previous studies indicated that family environment, especially parental, not institutional care and immaturity at birth, influenced children's psychological development (12-14). The present study aimed to consider DHA administration after birth in relation to the presence or absence of domestic, parental care during the first three years of life. Moreover, the objective was to evaluate whether the parenteral administration of lipid emulsion containing DHA could also modify or even compensate the newborn's immaturity effect on psychological development at three years of age. Specifically, the study aimed to examine the cognitive, linguistic, emotional, and social development of 3-year-old children who were born prematurely. Especially, if assumed that emotional development is the most important factor influencing language and cognitive development (15) it was also aimed to find if the parenteral administration of lipid emulsion containing DHA could modify these relations.

The current study focused on answering three main questions. First, it was asked whether an intake of DHA during the first days of life of prematurely born children may influence their psychological development at the age of three years. The second question was to evaluate whether the effect of this parenteral DHA support could not only be distant but also indirect, which means whether or not it can modify the influence of the presence or absence of domestic, parental care and immaturity at birth on the psychological development three years later. The third question was whether the parenteral administration of the lipid emulsion rich in DHA may modify the influence of emotional development on the

cognitive and linguistic development of three-year-old children born prematurely.

MATERIAL AND METHODS

A total number of 36 three-year-old children were tested: 20 boys and 16 girls (corrected age, M=38 months, SD=4.85). The children were born prematurely between 24 and 28 weeks of pregnancy, with very low birth weight (<1500 g; M=998 g, SD=207 g, Minimum=680 g, Maximum=1440 g).

An invitation to participate in this psychological study was sent to 68 parents whose children were born prematurely and hospitalized in the Department of Neonatology, Collegium Medicum, Jagiellonian University (11). Of the 68 parents invited, only 36 (52.9%) agreed to participate in the study and signed the consent form. From 1st November, 2010 to 30th June, 2011, the parents brought their children to the Laboratory of Child Development in the Institute of Psychology, Jagiellonian University, where each child was individually tested. On average, the testing session lasted 65 minutes.

Two groups of children were tested in the study, using a quasi-experimental design: the control group and the study group. The children in the control group, who had been parenterally given a standard lipid solution, were born between the 1st of October 2007 and the 31st of March, 2008. The children in the study group, who had been given parenteral nourishment with a modified fatty emulsion containing DHA, were born between the 1st of April and the 30th of September, 2008. The mean values of gestational ages in both groups were comparable but the values of the mean age of the children when they were tested were different (see: table I). The children in the study group were found to be significantly younger than those in the control group. They were supplemented parenterally with the lipid emulsion rich in DHA, during the first 3-4 weeks of life. The total dose of DHA they obtained parenterally ranged from 2 to 4 grams during this whole period of time.

At the beginning of the session, one of the parents was asked to complete the 15-item questionnaire that informed about the child's social environment (e.g. education of parents and type of child care – domestic or institutional care). To extract the aggregated index called "presence of domestic care", the first unrotated factor method (Factor Analysis) was used. This method made it possible to calculate the index which explained at least 50% of the variation of the variable. To calculate the index of variable "immaturity", medical documentation (e.g. APGAR score evaluated in the 5th minute of life, gestational age, birth weight etc. which are precisely described in study 11) was used. Also the index of "immaturity" was obtained through factor analysis and also by using the first unrotated factor method. The index of immaturity explained 50% of the variance of the whole variable and it was used in further analyses as the more valid index of the variable.

To measure dependent variables after the session, parents completed the Social-Emotional Scale (SES)[1] and the Adaptive Behavior Scale (ABS)[2] which are part of Bayley Scales of Infant and Toddler Development, Third Edition.[3] This was the way in which indexes of emotional and social development were obtained. Cognitive development was measured by the Children's Developmental Scale (16), which is the Polish version of the Bayley Scales of Infant and Toddler Development. The scale consists of 10 subscales: Manipulation, Perception, Scribbling and Drawing, Blocks, Comparing, Memory, Speech, Vocabulary, Social Behaviors, Motor Abilities. Language Development (i.e., vocabulary range) was measured by the Vocabulary Test – Comprehension[4] (17), a Polish version of the Peabody Picture Vocabulary Test.

The statistical analysis presented below was performed with the use of statistical modules of SPSS Statistics 21.PL package: Factor Analysis, t-test, Analysis of Covariance (ANCOVA), General Linear Model (GLM) with the analysis of interaction effects (MODERATION).

RESULTS

Table I presents the descriptive statistics for all the variables for the two groups of children: the study group (supplemented with DHA) and the control group (without DHA supplementation). The results of the inferential statistics that compares the two groups are also presented in table I.

Because the groups tested differed according to calendar age, two sets of analyses were conducted to determine if the parenteral administration of lipid emulsion rich in DHA contributed to differences in the psychological development of 3-year-old children, including cognitive, linguistic, emotional and social development. One set of analyses was controlled for age (analysis of covariance) and one was not controlled for age (t-tests). The results presented in table I showed that only the level of linguistic development was statistically different in the groups tested but this difference was no longer significant if controlled for age. The study failed to provide evidence that intravenous administration of lipid emulsion rich in DHA after birth contributed to differences in psychological development when a child was three years old. That is why the question of whether diet modifies the influence of other factors on the development of the child seems to be even more interesting.

To answer whether the parenteral administration of DHA immediately after a preterm birth influenced the psychological development of three-year-old children in

[1]This measure consisted of 28 questions (e.g. "Uses words or pictures to show you what she/he likes or dislikes"). The parent answered by pointing to the frequency of the described behavior. The response scale ranged from 0 = "difficult to say" to 5 = "all the time").
[2]The measure consisted of 10 subscales, containing a total of 723 items (e.g. "tries to makes friends with children of his/her age"). The parent answered on a scale of 0 to 3, with 0 being "I don't know," and 3 being "does this always, or almost always, when appropriate to do so."
[3]The measures were translated by Agnieszka Nowak in cooperation with the 0-5 Foundation, which was given permission by the editor to use the original version of the Bayley Scales to prepare the Polish adaptation of this world-renowned tool. The authors are grateful to Dr. Magdalena Stawicka and Dr. Magdalena Polaszewska-Nicke, who let us use these tools.
[4]The authors used an experimental version of the tool that is now published with Polish normative data. They are grateful to Dr. Ewa Haman, who provided this tool.

Table I. Descriptive and inferential statistics for variables tested in the study (SG) and control (CG) groups.

Tabela I. Dane opisowe oraz wyniki testu istotności różnic dla badanych zmiennych w grupie badanej (SG) i kontrolnej (CG).

Variables *Zmienne*	N		M (SD)		Range *(Minimum -Maximum)*		Without controlling for age *Bez kontroli wieku*			With controlling for age *Z kontrolą wieku*			
	SG	CG	SG	CG	SG	CG	t	df	p	dfE	dfB	F	P
Cognitive development *Rozwój poznawczy*	23	13	116.91 (16.24)	123.15 (18.34)	80-139	73-145	-1.06	34	0.298	1	33	0.12	0.728
Linguistic development *Rozwój językowy*	16	11	19.50 (10.87)	35.45 (17.99)	8-40	9-71	-2.88	25	0.008	1	24	0.90	0.351
Social development *Rozwój społeczny*	20	10	475.40 (64.54)	493.10 (67.17)	360-597	358-591	-0.70	28	0.490	1	27	0.94	0.341
Emotional development *Rozwój emocjonalny*	21	9	128.57 (10.70)	127.56 (8.96)	91-140	114-138	0.25	28	0.805	1	27	0.11	0.743
Home care *Opieka domowa – opieka w domu*	22	12	-0.04 (1.11)	0.16 (0.84)	-1.98-1.49	-1.11-1.49	-0.55	32	0.589	-	-	-	-
Immaturity at birth *Niedojrzałość przy narodzinach*	20	11	0.21 (0.96)	-0.37 (1.01)	-1.05-1.68	-1.61-1.40	1.58	29	0.124	-	-	-	-
Age *Wiek*	23	13	34 (5)	42 (5)	34-48	29-51	-4.68	34	<0.001	-	-		-

N – number of children tested, N – *liczba badanych dzieci,* M – mean, M – *średnia,* SD – standard deviation, SD – *odchylenie standardowe,* Range – range of the results (from minimum to maximum), Range – *zakres wyników (od minimum do maximum)*, t – t-test, t – *test t*, df – degree of freedom, df – *liczba stopni swobody*, p – level of significance, p – *poziom istotności*, F – analysis of variance test, F – *test analizy wariancji*

Table II. Results of the analysis of moderation (interaction effects between continuous and dichotomous variables). Predictor: Domestic care. Moderator: diet rich in DHA vs no diet rich in DHA.

Tabela II. Wyniki analizy moderacji (efekty interakcji między zmienną ciągłą a dychotomiczną). Predyktor: Opieka domowa – brak lub stała opieka w domu; Moderator: dieta bogata w kwasy DHA vs brak diety bogatej w DHA.

Dependent variable *Zmienna zależna*	β	BS	t	p
Cognitive development *Rozwój poznawczy*	-0.027	0.168	-0.160	0.874
Linguistic development *Rozwój językowy*	-0.242	0.186	-1.301	0.207
Social development *Rozwój społeczny*	-0.108	0.194	-0.555	0.584
Emotional development *Rozwój emocjonalny*	-0.112	0.194	-0.557	0.569

β standardised regression coefficient for the main analysis, β *standaryzowany współczynnik regresji*, BS: standard error, BS: *błąd standardowy*, t – t-test, t – *test t*, p – level of significance, p – *poziom istotności*

Table III. Results of the analysis of moderation (interaction effects between continuous and dichotomous variables). Predictor: immaturity at birth. Moderator: diet rich in DHA vs no diet rich in DHA.

Tabela III. Wyniki analizy moderacji (efekty interakcji między zmienną ciągłą a dychotomiczną). Predyktor: Niedojrzałość po narodzinach; Moderator: dieta bogata w kwasy DHA vs brak diety bogatej w DHA.

Dependent variable *Zmienna zależna*	β	BS	T	P
Cognitive development *Rozwój poznawczy*	-0.092	0.180	-0.510	0.614
Linguistic development *Rozwój językowy*	-0.220	0.172	-1.278	0.215
Social development *Rozwój społeczny*	0.078	0.199	0.390	0.700
Emotional development *Rozwój emocjonalny*	-0.469	0.187	-2.503	0.020*

β: standardised regression coefficient for the main analysis, β: *standaryzowany współczynnik regresji*, BS: standard error, BS: *błąd standardowy*, t – t-test, t – *test t*, p – level of significance, p – *poziom istotności*, *p<0.05

Table IV. Results of the analysis of moderation (interaction effects between continuous and dichotomous variables). Predictor: Emotional development; Moderator: diet rich in DHA vs no diet rich in DHA.

Tabela IV. Wyniki analizy moderacji (efekty interkacji między zmienną ciągłą a dychotomiczną). Predyktor: Rozwój emocjonalny; Moderator: dieta bogata w DHA vs brak diety bogatej w DHA.

Predictor *Predyktor*	Dependent variable *Zmienna zależna*	β	BS	t	p
Emotional development *Rozwój emocjonalny*	Cognitive development *Rozwój poznawczy*	0.170	0.185	0.922	0.365
	Linguistic development *Rozwój językowy*	0.352	0.169	2.086	0.049*

β: standardised regression coefficient for the main analysis, β: *standaryzowany współczynnik regresji*, BS: standard error, BS: *błąd standardowy*, t – t-test, t – *test t*, p – level of significance, p – *poziom istotności*, *p<0.05

relation to the presence or absence of domestic, parental care over three years and in relation to the immaturity at birth, a series of analyses of interaction was conducted. To analyze the interaction of the continuous variable with a dichotomous variable, the General Linear Model (GLM) was used (see: table II and III). In GLM the predictor, the moderator and their product were entered in the analysis. The significant effect of the product while controlling the impact of the predictor and the moderator was taken as proof of the interaction effect (18).

The parenteral administration of the lipid emulsion containing DHA did not modify the relation between the presence of domestic parental care and psychological development but did modify the relation between immaturity at birth and emotional development. To further analyze the interaction between immaturity and DHA intake, the regression between the predictor (immaturity at birth) and dependent variable (emotional development) was calculated separately for the two groups tested: those who did and did not take DHA. The standardised Beta coefficient for the results in the group without the DHA nourishment was significant ($\beta=0.53$, $p<0.05$) but was not significant for the group with the DHA diet ($\beta=-0.48$, $p>0.05$). In other words, if children were without the diet modification, the relation between immaturity at birth and emotional development was observed but in children who intravenously obtained an intake of DHA, this relation was not observed. If we assume that immaturity at birth inhibits emotional development, the fact that the relation between immaturity and emotional development was not observed in children with a diet rich in DHA seemed very important. It is suggested that this diet may have a compensatory influence on the relation between immaturity at birth and emotional development. The presence of DHA administered parenterally in the nourishment within the first weeks of life might alleviate the influence that a more severe health status present at birth (high degree of immaturity) has on the emotional development evaluated three years later.

The last hypothesis evaluated during the study was whether the administration of the lipid emulsion rich in DHA may modify the relation between children's cognitive and language abilities and their emotional development. An analysis of moderation was also conducted, assuming that emotional development was a predictor, diet was a moderator and cognitive and linguistic developments were dependent variables (see table IV).

The results obtained suggest that the answer to the third question was positive but only for the relation between emotional and linguistic development. It

turned out that the parenteral administration of DHA during the first weeks of life modified the relation between emotional and linguistic development in three-year-old children in a statistically significant way. To further analyze the interaction between emotional development and DHA intake, the regression between the predictor (emotional development) and dependent variable (linguistic development) was calculated separately for the two groups tested: those who did and did not take DHA. The standardised Beta coefficient for the results in the group with the DHA nourishment was significant (β=0.74, $p<0.05$) but was not significant for the group without DHA diet (β=-0.03, $p>0.05$). In other words, only in children who were nourished parenterally with the lipid emulsion containing DHA did emotional development influence linguistic development. A distant and indirect effect of the diet was observed, which could support the influence of emotional development on the child's linguistic abilities. A similar relation was not observed for cognitive development.

DISCUSSION

The results obtained in the study confirm that both biomedical and social factors have a considerable effect on the psychological development of children with very low birth-weight. Even after three years, these factors may still interact with each other to create a complex system of dynamically changing conditions. These findings provide partial support for the dynamic systems theory (6), which attempts to explain the complexity of these developmental processes.

The analyses of covariance indicated that a diet rich in DHA had no direct influence on psychological development. We suspect that this result might be associated with age differences between the groups tested when the children were about three years of age. This difference in calendar age was probably associated with a number of developmental differences between the two groups of children, which may not have been sufficiently controlled by statistically controlling for age. However, it has been seen later and the effects of interaction indicated that diet did have an influence on psychological development in certain circumstances.

The current study makes several important contributions to research on the psychological development of infants who are born prematurely. First, it showed that with the modification in child nourishment after birth, meaning a diet rich in DHA, the relation between immaturity at birth and emotional development can be modified. If there is a risk factor, such as a poor health condition after birth, and it could influence the emotional development during later years, it may be suspected that this relation would not be obvious in children who were fed parenterally with the lipid emulsion containing DHA. This distant and indirect effect of a diet rich in DHA was only observed for emotional development but was not important as far as linguistic, cognitive and social development was concerned. Perhaps the domain of emotional development is the first and most sensitive factor to the influence of DHA or perhaps the groups tested were not large enough to observe other significant effects.

No modifying effect of the diet rich in DHA on the relation between the presence of parental care and the psychological development of the tested children was observed. This result should serve as motivation to search for more reliable techniques to measure parental care, as there are many studies indicating the important role of home environment in preterm child development (19-21). We would like to emphasize that the short questionnaire in the present study could not describe parental care in detail.

The modifying effect of a diet rich in DHA on the relation between emotional and linguistic development was also shown. In children parenterally fed with an emulsion containing DHA within the first weeks after birth, the influence of emotional development on linguistic development was observed. This made it possible to suggest that DHA administration after birth seems to be a latent factor, which might have an important effect on later development. At the age of three years, these children with a diet rich in DHA were more likely to develop linguistic abilities, because of their emotional development. On the grounds of these results it can be suggested that a diet rich in DHA might be a protective and latent factor that makes the child emotionally stable, which provides a better environment for their linguistic development. Although these results seem to be very interesting, they should be treated with caution, because they were obtained from a study on a relatively small group of children. The results should be verified in multicenter prospective randomized and controlled studies, especially controlling for the age of the children tested. Another important fault of the present work is the lack of information about the intake of DHA in the tested children via natural nutrition (in 2008 the children's intake included a small amount of DHA with an artificial food compound but both groups of children were breastfed: 91% of the children in the study group and 87% in the control group and neither the mothers' diet and nor the time of breastfeeding was controlled). This should also be controlled in further research.

CONCLUSIONS

The present study indicates that an appropriate modification of parenteral nourishment, meaning a diet rich in DHA, seems to be important as a protective factor for prematurely born children. This factor might be seen as a latent variable, having indirect and distant effects on child development after even three years. The proposed mechanism of this influence is the supportive effect of the nourishment on the child's emotional development. The immaturity of a child at birth seems to affect his/her emotional development when the infant is not nourished with DHA. Moreover, this stable emotional development even after three years, can influence linguistic development. When DHA is provided parenterally during the first weeks of life, it significantly supports the child's psychological development. However, further research to verify these findings should be conducted with larger, randomized groups of children and should also be planned as a series of follow-up studies.

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Address for correspondence:
Marta Białecka-Pikul
Instytut Psychologii, Uniwersytet Jagielloński
Al. Mickiewicza 3, 31-120 Kraków
tel. 519-516-453
e mail: marta.bialecka-pikul@uj.edu.pl