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Evaluation of cardiac status in children with intestinal failure on long-term parenteral nutrition

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HIGHLIGHTS

- Children on long-term parenteral nutrition have thicker interventricular septum wall.
- Interventricular septum wall thickness correlates with glucose supply in parenteral nutrition.
- Resembling the situation of hypertrophic cardiomyopathy in infants of diabetic mothers.

1. Introduction

Long-term parenteral nutrition is an effective method of treatment preventing malnutrition and giving children with intestinal failure a chance for survival and normal development [1], however it is related to several complications. The most known and frequent ones are catheter-related sepsis, thrombosis, parenteral nutrition related liver disease, osteoporosis [2]. Circulation complications of long-term parenteral nutrition (PN) have not been widely explored. Until now, no studies assessing cardiac status in patients with intestinal failure obtaining long-term parenteral nutrition have been performed. Hypothetically there are several factors which might influence cardiac status in children with intestinal failure on long term parenteral nutrition, such as: volume overload, due to the necessity for compensation for fluid losses from intestinal tract, especially in children with stomias before restoring intestinal continuity, volume overload, due to technical factors in preparation process of nutrition mixtures necessary to maintain their chemical stability, presence of a permanent central catheter in right atrium, catheter-related sepsis in patient's medical history potentially affecting multiple organs, nutritional deficiencies such as: carnitine, ferrum, anemia, vitamin D, metabolic influence of administered nutrition mixtures.

The aim of the study was to evaluate the cardiac status in children with intestinal failure on long-term parenteral nutrition and to identify factors related to this medical condition and it's treatment, that might influence the circulation system.

2. Material and methods

2.1. Study design

The research was designed as a cross-sectional observational study. The inclusion criteria were intestinal failure and treatment with long-term parenteral nutrition according to the ESPEN/ESPGHAN guidelines in HPN program for at least 3 months. The exclusion criteria were: known cardiac disease, known chronic disease, that might influence cardiac status (such as cystic fibrosis). The examination were performed during a control visit in our Out-Patient Nutrition Clinic in the optimal state of health of participants (any acute aberration of health state caused by infections, metabolic instability etc. caused postponement of examination).

2.2. Ethics

This study was ethically approved by the Bioethical Committee of Children's Memorial Health Institute. Written informed consent was obtained from parents and patients aged 16 years and more.

2.3. Methods and statistical analyses

Nutritional status of patients was evaluated with anthropometric measurement, on the base of which body mass index was calculated, and laboratory examination of the serum concentration of ferrum, vitamin D3, albumins, carnitine and hemoglobin blood concentration.

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Table 1
Incidence of nutrient deficiencies in the studied group.

	Fe < 59 µg/dl	25OHD3 < 30 ng/ml	Carnitine < 42 µmol/ml	Hgb < normal values limits for age	Alb < 38 g/l
% of patiens with deficiences	55	63	70	55	10

Characteristics of parenteral nutrition in the studied group are presented in Table 2.

Table 2
Characteristics of parenteral nutrition in the studied group.

	Days of PN per week	Hours of PN per day	Ml of PN per hour	Ml of PN per kg per day	Lipids in PN (g) per kg per week	Dextrose in PN (g) per kg per day	Aminoacids in PN (g) per kg per day
Mean (range)	5,48 (2–7)	12,8 (10–19)	107,7 (43–293)	69,5 (14–171)	7 (1,3–14,7)	9,8 (2–17,5)	1,48 (0,25–2,65)

The cardiac status was evaluated by basic diagnostic cardiological tests (chest X-ray with assessment of cardio-thoracic ratio, standard echocardiography with assessment of basic functional and structure parameters, measurement of peptide NTproBNP serum concentration).

Echocardiography (2D; M-mode, Doppler) was performed by specialized pediatric cardiologist echocardiographer using a Philips iE33 ultrasound machine with appropriate transducers (8 or 5 MHz). Each participant underwent echocardiography in accordance with the standard images and techniques presented in the American and European Echocardiography Society guidelines [3]. Based on echocardiography basic M-mode structural parameters (LVDd-left ventricular end diastolic dimension, IVSd - thickness of interventricular septum at end diastole, LVPW left ventricular posterior wall thickness at end diastole, RVDd right ventricular end diastolic dimension), systolic parameters (left ventricle shortening fraction) and diastolic parameters (flow waves E to A ratio through atrio-ventricular valves) were assessed. All echocardiographic structural parameters were indexed to body surface area (BSA) and expressed as z-score for BSA, after comparing with normal values established on the base of epidemiological studies [4]. The mean z-scores for all measured parameters in the studied group were calculated. Observed differences between the z-scores of the studied group and population normal values based on 2036 healthy European children [4] were statistically analyzed by T-student test. A p value below 0,05 was considered as statistically significant. The results were also expressed as a percentage of abnormal values (< / > 2SD) in the studied group.

The functional parameters were defined as abnormal, if exceeded the established normal limits, that is 28–44% for left ventricle shortening fraction, and 1–2,8 for E/A ratio [5]. The results were expressed as a percentage of abnormal values (< / > normal limits) in the studied group.

In each patient a posterior-anterior chest X-ray was performed with assessment of cardio-thoracic ratio - the ratio of maximal horizontal cardiac diameter to maximal horizontal thoracic diameter. The ratio above 0,5 was defined as abnormal [5]. Results were expressed as a percentage of abnormal values in the studied group.

In each patient serum concentration of NT-pro-BNP – a well documented biochemical marker of heart failure [6] – was assessed with the use of electrochemiluminescence immunoassay kit (Cobas h232, Roche Diagnostics (Basel, Switzerland)). Results were compared with normal values established on the base of epidemiological studies [7] and defined as abnormal, if the result was above 95th percentile for age – and then expressed as percentage of the upper normal limit. Percentage of abnormal values in the studied group was calculated.

Correlation of the cardiac results of the studied group with potential factors related to intestinal failure and parenteral nutrition such as: nutrients and fluid content in the mixture, fluid flow, frequency of PN administration per week, the period from initiating PN, hours of PN administration per day, nutrition status, carnitine, ferrum, hemoglobin and vitamin 25-OH D3 serum concentrations; were analyzed with Spearman correlation test. A p value below 0,05 was considered as statistically significant.

3. Results

3.1. Study population

Seventy one children (44 boys – 62%) with intestinal failure aged from 0,92 to 19,84 years (mean – 7,6 year), being already in the parenteral nutrition program for the mean of 4,9 years (0,66–14,75 years) were included in the study. The main cause of intestinal failure was short bowel syndrome (61 patients – 86%), in 5 patients – intractable diarrhea, in 3 patients – pseudoobstruction, in 2 patients - Crohn's disease.

The mean value of BMI in the studied group was 16,4 kg/m2 (range: 13–26), (the mean percentile for age was 29). Percentage of specific deficiencies defined as ferrum serum concentration below 59 µg/dl, vitamin D3 serum concentration below 30 ng/ml, carnitine serum concentration below level 42 µmol/ml, albumin serum concentration below 38 g/l, hemoglobin concentration below normal limits for age [8], stated in the studied group are presented in Table 1.

3.2. Echocardiographic results

3.2.1. Functional parameters

In the studied group, in most of the patients systolic function of left ventricle, expressed as shortening fraction, remained in the normal limits, except for 5 patients (7%) in which it was even above normal limits - > 44% (44,9–49,3%). Diastolic function of left ventricle assessed with the ratio E/A of the flow waves through bicuspid valve remained in the normal limits in all of the patients. Diastolic function of right ventricle expressed with the ratio E/A of the flow waves through tricuspid valve remained in the normal limits in all of the patients, except of 3 (4,5%), in which the ratio was below 1 (0,65–0,79).

3.2.2. Structural parameters

The mean z-score values for each measured structural parameter in the group were calculated. The results, expressed as mean z-score, range and percentage of abnormal results are presented in Table 3. The main aberration of the echocardiographic structural parameters was the enlargement of interventricular septum wall thickness – the mean z-score was significantly higher than in the control group ($p < 0,001$), and in 19% of the patients the values exceed 2 standard deviations.

Echocardiographic results are presented in Table 3.

3.3. Radiological results

Cardio-thoracic ratio assessed on the PA chest X-ray was augmented (> 0,5) in 44% patients, and the range of abnormal values was 0,52–0,61.

Table 3
Echocardiographic results.

	IVSd	LVDd	LVPW	RVDd	SF	E/A bi	E/A tri
	z-score						
mean	0,87	−0,09	0,1	0,21	37%	1,66	1,5
p	< 0,001	ns	ns	ns			
range	−1,53–3,87	−3,64–2,72	−2,3–3,69	−1,86–3,53	28,6–49,3	1,2–2,8	0,65–2,38
% of abnormal results							
Above limits	19	1,5	4,5	14	7	0	0
Below limits	0	8,7	1,5	0	0	0	4,5

IVSd, thickness of interventricular septum at end diastole; LVEDD, left ventricular end diastolic dimension; LVPWd, left ventricular posterior wall thicknessat end diastole; RVDD, right ventricular end diastolic dimension.

3.4. Biochemical results

The serum level of NTproBNP peptide was elevated above 95th percentile for given age in 32% of the patients. The abnormal results exceeded the upper normal limit for an average of 280%.

3.5. Correlations of cardiac results with factors related to parenteral nutrition and intestinal failure

The main aberrations of the cardiac status stated in the studied group was the enlargement of heart size (CTR > 0,5) on chest X-ray in 44% patients, elevation of peptide NTproBNP serum level above 95th percentile in 32% and augmentation of the interventricular septum wall thickness above normal limits in 19% patients (mean z-score-0,87; p < 0,001).

Those aberrations correlated mainly with the parenteral nutrition's frequency, with the parenteral nutrition solution's volume and with the dextrose supply. Table 4.

The diagnoses in the patients with thickened inter-ventricular septum (84% - short bowel syndrome, in 8% - pseudoobstruction, in 8% Hirshprung disease) did not differ from the distribution of diagnosis in the whole studied group.

4. Discussion

Long-term parenteral nutrition is an effective method of treatment in intestinal failure, however it is related to several complications. Until now the influence of long-term parenteral nutrition on circulation system has not been widely explored. In the literature there have been few reports regarding circulation complication of long-term parenteral nutrition such as: right atrial and superior vena cava thrombosis [9–11], endocarditis [9,10], catheter-tip thrombosis [11], acute heart failure due to thiamine deficiency [9], increase in pulmonary arterial pressure during lipid infusion in neonates [12], lipomatous hypertrophy of interatrial septum in adults [13]. However all of the mentioned studies were case reports or case series focused mainly on acute complications of parenteral nutrition concerning circulation system. Until now no studies assessing the general cardiac state in children on long-term parenteral nutrition have been performed in a larger group.

The main aberration of the echocardiographic structural parameters was the enlargement of interventricular septum wall thickness. There was a significant correlation between this parameter and the dextrose supply in parenteral nutrition. It might be parallel to the pathophysiological situation of neonates of diabetic mothers, in 25–46% of which there is asymmetric septal hypertrophy stated in echocardiography [14]. According to the literature the hypothesised cause of this abnormality in this population is the mothers hyperglycaemia causing hyperinsulinemia in neonates [15]. Insulin, known for its hypertrophic function, is suggested to be the direct factor causing interventricular hypertrophy. In our study we did not measure serum insulin concentration in our patients, however hyperinsulinemia during parenteral nutrition has been described in the literature both in adults and children [16,17]. We have measured glycaemia in our patients once during the observation – in the morning before the visit in the Out-Patient Clinic, that is usually at the end (in majority of the cases) of nutrition mixture administration. The results remained in the normal limits in all of the patients, however it does not exclude periods of hyperglycaemia and/or hyperinsulineamia during the parenteral nutrition mixture administration. Interventricular septal hypertrophy in neonates of diabetic mothers is known for its transient character and it resolves in most of the cases during first 2–6 months of life [18,19], as far as the exposition to the causing factor (mothers' hyperglycaemia) cease. In our studied group we found the correlation of the interventricular septum diameter with the intensity of parenteral nutrition – that is the dextrose supply in PN mixture, the frequency of PN administration (days per week), and not with the period from initiating PN (during which in most of the cases it was possible to diminish the PN's intensity), also suggesting that the problem of enlargement of interventricular septum diameter might be transient.

In our study the cardiac status of children with intestinal failure on long-term parenteral nutrition remained in the normal limits in almost all of the cases of measured standard echocardiographic functional parameters.

However an elevation of the peptide NTproBNP serum concentration indexed to age was frequently found in the studied group. It may not be in opposite to the normal results of echocardiographic functional parameter, as far as many studies before showed an earlier alteration in biochemical results than in echocardiographic parameters [20]. The enlargement of the heart size on chest X-ray was also frequently stated in our studied population. There was a significant correlation between both NTproBNP serum concentration (indexed for age) and CTR on X-ray and the parenteral nutrition dextrose content and nutrition mixture's volume indexed to body weight.

In our study we did not found significant correlations between the

Table 4
Correlations of cardiac results with factors related to PN and IF.

	PN/7	Ml/kg/d	h/24 h	lip/kg/w	Dex/kg/d	AA/kg/d	BMI	Hgb
NTproBNP		< 0,001 *0375*	ns	0,004 *0344*	< 0,001 *0491*	< 0,001 *0,42*	0,009–*0,37*	0,004–*0,284*
CTR	0,032 *0286*	< 0,001 *0395*	0,01 *0,384*	ns	0,008 *0329*	0,024 *0281*	ns	0,015–*0,315*
IVSd	0,024 *0233*	0,014 *0306*	0,011 *0328*	ns	0,024 *0273*	ns	ns	ns

Upper row – p; lower row (*italics*) – r-Spearman's rank correlation.

nutritional status and cardiac results, except for a significant inverse correlation between the body mass index and NTproBNP serum concentration indexed for age. In the literature such inverse correlation has been already described in adults [21]. There also have been studies documenting high NTproBNP concentration in malnourished children [22]. In our studied population of children with intestinal failure the nutritional status was not optimal – the mean BMI value in the group was 16,4kg/m2, and was below 2SD for age in 16% of the cases. However only 26% of patients with elevated NTproBNP value had BMI under 3rd percentile. On the other hand, lower BMI in children with intestinal failure leads usually to the necessity for more intense parenteral nutrition. Positive correlation of PN's intensity (expressed as PN's frequency, nutrient content in PN's mixture) with NTproBNP serum concentration was found in our study. Tough the correlation between BMI and the NTpoBNP serum concentration might be indirect.

Although specific nutrient deficiencies, known for influencing the cardiac status from previous studies [23–28], were frequent in our studied population (from deficiency of ferrum in 55% cases to deficiency of carnitine in 70% of the cases), we did not found any correlation of serum concentration of those substances with any measured cardiac parameter. An explanation might be that, however frequent the deficiencies are in our group, there are not as advanced as in the cited studies.

Results of our study suggest that the cardiac status of children with intestinal failure on long-term parenteral nutrition is more affected by the treatment than by the nutrition status itself.

The main factors related to parenteral nutrition affecting cardiac status in children with intestinal failure might be high dextrose content in parenteral nutrition mixture and it's volume.

5. Conclusions

The main aberrations of the cardiac status stated in the studied group was the enlargement of heart size on X-ray, elevation of peptide NTproBNP serum concentration and augmentation of the interventricular septum wall thickness above normal limits assessed on echocardiography.

Those aberrations correlated mainly with the parenteral nutrition's frequency, with the parenteral nutrition mixture's volume and with the dextrose supply in parenteral nutrition.

Statement of authorship

JFG conceived and designed the study, with contributions from all co-authors. JFG and MMM collected the clinical data. JBK conducted the statistical analyses, and all authors participated in data interpretation. JFG drafted the article, and all authors contributed to revisions and final approval of the submitted manuscript.

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Conflicts of interest

None.

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