

Parenteral nutrition in patients with inborn errors of metabolism – a therapeutic problem

L. KALUZNY, M. SZCZEPANIK, Z. SIWINSKA-MROZEK, M. BORKOWSKA-KLOS¹, W. CICHY, J. WALKOWIAK

Department of Pediatric Gastroenterology and Metabolism, I Chair of Pediatrics, Poznan University of Medical Sciences, Szpitalna, Poznan, Poland

¹Department of Newborns' Infectious Diseases, Chair and Department of Neonatology at Poznan University of Medical Sciences, Poznan, Poland

Abstract. – BACKGROUND: Parenteral nutrition is now a standard part of supportive treatment in pediatric departments. We describe four cases in which parenteral nutrition was extremely difficult due to coincidence with inborn errors of metabolism. The first two cases were fatty acid β -oxidation disorders associated with necrotizing enterocolitis and congenital heart disease. Thus, limitations of intravenous lipid intake made it difficult to maintain a good nutritional status. The third case was phenylketonuria associated with a facial region tumour (rhabdomyosarcoma), in which parenteral nutrition was complicated because of a high phenylalanine content in the amino acid formulas for parenteral nutrition. The fourth patient was a child with late-diagnosed tyrosinemia type 1, complicated with encephalopathy – during intensive care treatment the patient needed nutritional support, including parenteral nutrition – we observed amino acid formula problems similar to those in the phenylketonuria patient.

Parenteral nutrition in children with inborn errors of metabolism is a rare, but very important therapeutic problem. Total parenteral nutrition formulas are not prepared for this group of diseases.

Key Words:

Inborn errors of metabolism, Phenylketonuria, Tyrosinemia, Fatty acid oxidation, Parenteral nutrition, Malnutrition.

Introduction

Parenteral nutrition (PN) is now a standard part of supportive treatment in pediatric departments for patients undergoing intensive therapy or perioperative treatment, but the use of PN is not void of the risk of serious complications. These complications can be septic, metabolic and related to vascular access, and can be life threatening, but PN gives major benefits, especially during catabolic processes¹.

Inborn errors of metabolism are a group of genetically-determined disorders in which a specific enzyme defect produces a biochemical block that may have pathological consequences. In this group of diseases the patient sometimes needs special nutritional treatment, such as the avoidance of fasting and contraindication for lipid infusion in fatty acid oxidation disorders (FAOD). In aminoacidopathies, protein restriction and an amino acid mixture supplement is needed – potential formula should not contain amino acids, whose breakdown is blocked (e.g. phenylalanine in phenylketonuria)². We describe four cases treated in our department, in which PN was extremely difficult because of coincidence with inborn errors of metabolism. PN formulas are not prepared for this group of diseases because they contain amino acids which are prohibited in aminoacidopathies or have incorrect lipid profile in FAOD.

Methods

Case Histories

Case Report 1 – Long-chain Hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency Associated with Necrotizing Enterocolitis

A boy, JK, born 18 May 2013 preterm on 35 week of gestation, the Apgar score was 9, birth weight 2020 g. LCHAD deficiency was diagnosed based on expanded neonatal screening program at 3 week of life. At this moment patient was in good clinical condition; clinical symptoms of LCHAD deficiency were not observed. Dietary treatment: frequent meals with limitation of long-chain triglycerides (LCT) and supplementation of medium-chain triglycerides (MCT) was introduced. After 8 days general condition deteriorated rapidly, vomiting episodes and bleeding diarrhea were ob-

served. Based on X-ray and USG examination necrotizing enterocolitis (NEC) diagnosis was confirmed, pharmacotherapy (antibiotics) was started. After 3 days, because of intestinal perforation, surgical repair was needed. During perioperative period (2 weeks) enteral feeding was stopped – the patient received total PN with adequate glucose i.v. administration (about 10-11 mg/kg BW/min., control glycaemia in normal range), but, because of prohibition of intravenous lipids intake, energy intake was only 71-83 kcal/kg BW/day (expected – 120 kcal/kg BW/day). Nutritional status was not improving – respective body weight was 3230 g, 3140 g and 3220 g at surgery, 7 and 14 days thereafter. After this period enteral nutrition was restarted and – with cessation of PN – at this moment energy intake rose to 103 kcal/kg BW/day. Clinical and nutritional status improved, body weight was adequate for age (4850 g at 3 months).

Case Report 2 – Short-chain Dehydrogenase (SCAD) Deficiency Associated with Congenital Heart Disease

A girl, AK, born on 1 January 2005 after a full-term uncomplicated pregnancy to a healthy mother with four living children; the Apgar score was 9, and neonatologists observed only hypotrophy (birth weight 2020 g) at birth. Clinical findings in the neonatal period were hypotonia, vomiting, poor feeding, failure to thrive and loud systolic murmur.

Ventricular septal defect type II (VSD II) was diagnosed based on typical clinical symptoms and echocardiography (“Swiss cheese” type). The patient was qualified for cardiac surgery with extracorporeal circulation. Preoperative management of this child required improving its nutritional status. The patient needed an energy intake of about 140 kcal/kg BW/day. Because of its failure to thrive and severe form of malnutrition (2740 g body weight at 11 months), the patient was sent to the our Department. At the moment of admission elevated aminotransferases activities (AST 793 U/L and ALT 260 U/L) were observed. Selective screening tests for inborn errors of metabolism – elevated C4-carnitine (23 μ mol/L) in the acylcarnitine profile by tandem mass spectrometry (MS/MS) and ethylmalonic aciduria in urine organic acids analysis (GC/MS) indicated a classic or variant SCAD deficiency. We introduced treatment – avoiding fasting and a low-fat diet.

Ensuring the child’s adequate nutrition in the pre- and perioperative period was extremely difficult due to the contraindication for administer-

ing lipids i.v. intake by patients with SCAD deficiency. We administered only 64.4 kcal/kg BW/day from the PN with excluded lipid intake. We tried to deliver the rest of the energy and other macro- and micronutrients *via* enteral feeding (hydrolysate formula with added maltodextrin). The patient received adequate macronutrient and trace element intake, but the energy intake was only 125 kcal/kg BW/day as opposed to the expected 140 kcal/kg BW/day. Although the energy supply was insufficient the patient’s nutritional status improved, and after 6 weeks (by 3300 g body weight) surgical repair was performed with extracorporeal circulation (VSD Dacron patch). Postoperative treatment was complicated by disseminated intravascular coagulation and sepsis. During this period we observed analogical nutritional problems but with reduced energy expenditure (110 kcal/kg BW/day). After 23 days enteral nutrition tolerance improved and PN was ended. Since then we did not observe any hemodynamic abnormalities, and both nutritional status and psychomotor development were improving.

Case Report 3 – Phenylketonuria Associated with Rhabdomyosarcoma

A girl, AC, was born on 30 May 2006 after a full-term uncomplicated pregnancy to a healthy mother; the Apgar score was 9, body weight at birth was 2340 g. Phenylketonuria (PKU) was diagnosed based on a neonatal screening, differential diagnostic procedures of hyperphenylalaninemia confirmed the classical form of PKU. A low-Phe diet with a special formula – l-amino acid mixture was introduced. We observed normalization of the Phe concentration in the blood. The child’s physical and psychomotor development was normal.

At the age of 18 months we observed a tumour in the buccal facial region. A CT scan was typical for rhabdomyosarcoma, and a tumour biopsy confirmed the diagnosis (embryonal rhabdomyosarcoma). Administering enteral nutrition was extremely difficult due to the tumour’s localization and due to the patient’s psychological problems connected with gastro-nasal tube tolerance. We introduced PN procedures. This form of nutritional treatment was difficult to introduce because of the high Phe content in the amino acid mixtures for PN. We used the Aminosteril N-Hepa 8% mixture as a source of amino acids because it has a lower Phe content than Aminoven 6% and/or Primene 10%. The Phe

concentration in the blood (fluorometric method) was elevated (15 mg/dL). After two weeks we introduced enteral nutrition procedures and observed normalization of the Phe concentration. Due to the short time period of PN treatment and the hyperphenylalaninemia status we did not observe brain damage and psychomotor retardation, but after a 1 year remission metastasis of rhabdomyosarcoma was diagnosed, and the patient died following 3 months of therapy.

Case Report 4 – Tyrosinemia Type 1 Complicated with Encephalopathy

A boy, NM, was born on 4 September 2011 (3 weeks before expanded newborn screening using MS/MS in the Wielkopolska region was introduced) after a full-term, uncomplicated pregnancy; the Apgar score was 10, body weight at birth was 3640 g. At the age of 8 months hepatomegaly and coagulopathy were started. The alpha-fetoprotein (AFP) level was very high: 21172.0 ng/mL. The diagnosis was based on selective screening tests (MS/MS – elevated tyrosine, methionine, ornithine, citrulline and arginine, GC/MS – high levels of urinary p-hydroxyphenylacetic, hydroxyphenylacetic, p-hydroxyphenylpyruvic and 6-hydroxy-4-ketoheptane acids). Nitisone and dietary treatment were started, but due to a severe clinical condition patient needed ventilator support and total (for 3 weeks) then later partial PN. The latter was difficult due to the same problem as in the previous case of the PKU patient, as there was a high level of Phe and Tyr in the amino acid mixtures for parenteral nutrition. In the parenteral nutrition we used an Aminosteril N-Hepa 8% amino acid mixture. For the first few weeks we administered a low protein intake (0.3 g/kg BW/day). After 3 weeks we introduced enteral feeding using a 1-amino acid formula (Tyr Anamix Infant, SHS). During the decompensation period, due to coagulopathy and liver insufficiency, the patient developed ischemic lesions in the brain resulting in encephalopathy and severe psychomotor retardation. Today the patient is fed orally with a 1-amino acid mixture and low protein food, Tyr levels are in the recommended range.

Discussion

Case reports of children with total parenteral nutrition associated with inborn errors of metabolism are extremely rare. In last years 3 PKU chil-

dren treated with PN were reported. The first child described by Lin was a 1890 g newborn on PN, Phe levels rose 5 times faster in this case and resulted in extremely high Phe levels³. The second was a 6-year-old boy with classical PKU who was diagnosed with Burkitt's lymphoma – metabolic control during chemotherapy was achieved by using a parenteral custom-made amino acid solution, yet about 70% of the control Phe levels continued to be abnormal⁴. The third case was a very preterm infant born at 27 week of gestation. In this case the authors reported a lack of Phe – free amino acid solution for PN. For PN mixture preparation in this situation was used, like in our patient with PKU and rhabdomyosarcoma, Aminosteril N-Hepa 8% – amino acids solution with lower content of phenylalanine⁵.

Non-PKU patients with an inborn error of metabolism who were administered PN were not reported, but especially fatty oxidation defects and aminoacidopathies with necessity of PN seem to be extremely difficult cases.

Mitochondrial beta-oxidation plays a major role in energy production, in particular during periods of fasting. Typical clinical symptoms of FAOD are as follows: hypoketotic hypoglycaemic coma, liver failure, cardiomyopathy, encephalopathy, sudden death^{2,6}. Treatment is only symptomatic, it is important to avoid fasting and to use a low-fat and carbohydrate-rich diet; also, intravenous lipids are not to be administered. Patients with FAOD need special perioperative treatment (including high-dose glucose infusion)⁸.

Necrotizing enterocolitis (NEC) may affect any part of the gastrointestinal tract but the most common sites are terminal ileum, caecum, ascending colon. It is a transmural disease with a bowel wall pneumatosis as the most typical appearance. Numerous ethiological factors are recognized although the dominant are gut hypoxia, microbial translocation, enteral nutrition. It's diagnosis is rather easy if supported by an X-ray examination. Treatment may be medical only or up to surgical intervention⁹.

VSD II is the most common congenital cardiac anomaly. The multiple muscular ventricular septal defect is called a "Swiss cheese" type. Infants with VSDs have substantially higher (40%) total energy expenditure than healthy infants¹⁰.

In the preoperative treatment of children with FAOD and associated congenital heart disease or NEC, strong contraindication for lipids i.v. intake makes it difficult to maintain a good nutritional status and to avoid perioperative complications.

PKU (OMIM 261600) is the most frequent in-born error of amino acid metabolism caused by deficiency of the phenylalanine hydroxylase enzyme (PAH) (hydroxylation of Phe to Tyr). Untreated or poorly controlled PKU results in severe brain damage with mental retardation (developmental/intelligence quotient 20-40), autistic behaviour, seizures. The PKU patients' diet is restricted in natural proteins, and patients consume a l-amino acid mixture with vitamin and mineral supplements⁶.

Rhabdomyosarcoma is a soft tissue malignant tumour of skeletal muscle origin. RMS is a relatively rare form of cancer. Diagnosis is based on tumour biopsy, and treatment consists of chemotherapy, radiation therapy and surgery. This combined therapy offers good prognosis. Patients with metastasis have a poor chance for long-term survival¹¹.

The coincidence of PKU and RMS can result from catabolic processes in the tumour in elevated Phe levels. The lack of an amino acid mixture with an elimination of Phe makes prevention of the hyperphenylalaninemia status difficult and has a negative influence on brain development and prognosis.

Tyrosinemia type 1 (OMIM 276700) is an in-born error of amino acid metabolism caused by deficiency of the fumarylacetoacetate hydrolase enzyme (FAH). Deficiency of FAH activity results in a metabolic block in the degradation pathway of tyrosine and produces an accumulation of precursor products – fumarylacetoacetate and maleylacetoacetate, which are hepato- and nephrotoxic^{2,6}. The necessity of PN in tyrosinemia type 1 patients caused the same metabolic problems as in PKU and had a negative influence on liver function and long-time prognosis.

Today the incidence of metabolic diseases is not so high but the recent use of tandem mass spectrometry (MS/MS) has allowed for changes in traditional newborn screening services, thus, leading to expansion and improvement of testing⁷. In the next years we will probably observe an increasing number of diagnosed children. Because of this situation we must be prepared for patients with a coincidence of inborn errors of metabolism and other rare disorders – including diseases in which patients will need PN procedures.

Conclusions

Parenteral nutrition in children with inborn errors of metabolism is rarely needed but it

does constitute a very important therapeutic problem – parenteral nutrition formulas are not prepared for this group of diseases. Nutritional and metabolic control of these patients still remains a challenge.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

- 1) GHABRIL MS, ARANDA-MICHEL J, SCOLAPIO JS. Metabolic and catheter complications of parenteral nutrition. *Curr Gastroenterol Rep* 2004; 6: 327-334.
- 2) ZSCHOCKE J, HOFFMANN GF. *Vademecum metabolicum*, 3th edition. Milupa/Schattauer, Friedrichsdorf, 2011.
- 3) LIN HJ, KWONG AM, CARTER JM, FERREIRA BF, AUSTIN MF, DEVARAJAN K, COLEMAN RJ, FEUCHTBAUM LB, LOREY F, JONAS AJ. Extremely high phenylalanine levels in a newborn on parenteral nutrition: phenylketonuria in the neonatal intensive care unit. *J Perinatol* 2011; 31: 507-510.
- 4) SALVARINOVA-ZIVKOVIC R, HARTNETT C, SINCLAIR G, DIX D, HORWATH G, LILLOQUIST Y, STOCKLER-IPSIROGLU S. The use of parenteral nutrition for the management of PKU patient undergoing chemotherapy for lymphoma: a case report. *Mol Gen Metabol* 2012; 105: 571-574.
- 5) BALLHAUSEN D, EGLI D, BICKLE-GRAZ M, BIANCHI N, BONAFE L. Born at 27 weeks of gestation with classical PKU: challenges of dietetic management in a very preterm infant. *Ped Rep* 2011; 3: 103-107.
- 6) ONLINE MENDELIAN INHERITANCE IN MAN OMIM (2013) Phenylketonuria (261600), tyrosinemia t. 1 (276700), LCHAD deficiency (609016), SCAD deficiency (201470) Accessed 1 February 2014.
- 7) BURGARD P, RUPP K, LINDNER M, HAEGE G, RITGER T, WEINREICH S, LOEBER JG, TERUSCIO D, VITOZZI L, CORNEL MC, HOFFMANN G. Newborn screening programmes in Europe; arguments and efforts regarding harmonization. Part 2 – From screening laboratory results to treatment, follow-up and quality assurance. *J Inher Metab Dis* 2012; 35: 613-625.
- 8) TURPIN B, TOBIAS JD. Perioperative management of a child with short-chain acyl-CoA dehydrogenase deficiency. *Paediatr Anaesth* 2005; 15: 771-777.
- 9) NEWELL SJ. Gastrointestinal disorders. In: Janet M, Rennie MA, eds. *Roberton's Textbook of Neonatology*, 2010; pp. 695-703.
- 10) ACKERMAN IL, KARN CA, DENNE SC, ENSING GJ, LEITCH CA. Total but not resting energy expenditure is increased in infants with ventricular septal defects. *Pediatrics* 1998; 102: 1172-1177.
- 11) RODEBERG D, PAIDAS C. Childhood rhabdomyosarcoma. *Semin Pediatr Surg* 2006; 15: 57-62.