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RESEARCH REPORT

Nutritional and Pharmacological Management during Chemotherapy in a Patient with Propionic Acidaemia and Rhabdomyosarcoma Botryoides

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Abstract We present the nutritional and pharmacological management of a 2-year-old girl with a severe form of propionic acidaemia and a genitourinary embryonal rhabdomyosarcoma. This association has not been described before, nor the utilization of chemotherapy in patients with propionic acidaemia.

The patient is a girl with neonatal onset of propionic acidaemia, homozygous for the c.2041-2924del3889 mutation in *PCCA* gene. At 23 months of age she was diagnosed with genitourinary embryonal rhabdomyosarcoma. Conservative surgery, brachytherapy and nine cycles of chemotherapy with iphosphamide, vincristine and actinomycin were recommended by oncologists. Due to the possibility that the child could present decompensations, we elaborated three different courses of treatment: when the patient was stable (treatment 1), intermittent bolus feeding through gastrostomy, containing 70 kcal/kg/day and 1.4 g/kg/day of total protein (0.6 g/kg/day of natural protein and 0.8 g/kg/day of amino acid-based formula) was prescribed; on the chemotherapy-days (treatment 2), diet consisted on continuous feeding, with the same energy and amino acid-based formula but half of natural protein intake; in case of decompensation (treatment 3), we increased by 10% the energy intake, and completely stopped natural protein in the diet but maintaining the amino acid-based formula. On chemotherapy- days carnitine was increased from 100 mg/kg/day to 150 mg/kg/day, and N-carbamylglutamate was added.

Through the 7 months with chemotherapy the patient did not suffer decompensations, while she maintained good nutritional status.

Enteral continuous feeding by gastrostomy, amino acid-based formula, and preventive use of N-carbamylglutamate during chemotherapy-days are the principal measures we propose in these situations.

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Sentence Summary This article describes, for the first time, the management of a patient with propionic acidaemia through 7 months with chemotherapy. Enteral continuous feeding, amino acid-based formula, and preventive use of N-carbamylglutamate during the days of chemotherapy are the principal measures we propose in these situations.

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Abbreviations

CEF	Continuous enteral feeding
EPSSG	European Pediatric Soft Tissue Sarcoma Study Group
IVA	Iphosphamide, vincristine, actinomycin
NCG	N-carbamylglutamate
OLCFA	Odd-numbered long-chain fatty acids

PA Propionic acidaemia
PCC Propionyl CoA carboxylase
RMS Rhabdomyosarcoma

Introduction

Propionic acidaemia (PA, OMIM 606054) is an autosomal recessive disorder caused by propionyl CoA carboxylase deficiency (PCC, EC 6.4.1.3) (Fenton et al. 2001). PCC converts propionyl-CoA formed in the catabolism of isoleucine, valine, methionine, threonine, odd-chain fatty acids, cholesterol side chains, thymine and uracil to methylmalonyl CoA (Ogier de Baulny et al. 2012). PA results from mutations in the *PCCA* (MIM 232000) or in the *PCCB* (MIM 232050) genes (Ugarte et al. 1999). Commonly, patients with PA present in the neonatal period with severe metabolic encephalopathy or early in infancy with failure to thrive, metabolic acidosis, developmental delay and various neurological symptoms (Sass et al. 2004). The mainstay of the long-term treatment is a low-protein diet supplemented with amino acids omitting the propiogenic ones, and avoidance of fasting to limit oxidation of odd-chain fatty acids (Ogier de Baulny et al. 2012). In spite of intense medical therapy most patients, especially those with a severe neonatal-onset form, have a high risk of relapsing episodes of acute metabolic decompensation, triggered by intercurrent stressing events such as fever, vomiting, fasting or infections. During acute intermittent illnesses, high-energy feeds without the precursor amino acids are required to prevent metabolic decompensation (Ogier de Baulny et al. 2005; McDonald et al. 2007; Deodato et al. 2006). The prognosis of PA has been improving in the last years, with a larger amount of patients reaching adult life (Martín-Hernández et al. 2009; Pérez-Cerdá et al. 2000; Baumgartner et al. 2007; Williams et al. 2009).

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma found in children (McDowell 2003). Sarcoma botryoides is an embryonal type of rhabdomyosarcoma that typically presents as a polypoid mass protruding from the vagina. Over the years there has been a shift in its treatment from radical surgery to a multimodal approach including conservative surgery, chemotherapy and radiotherapy. This approach has been associated with a 70% survival rate and a preservation of normal anatomy and function (Maharaj et al. 2008).

The association of PA and rhabdomyosarcoma botryoides has not been described before, nor has the utilization of chemotherapy in patients with PA. In these cases, side effects of chemotherapy, like vomiting, fasting, and recurrent infections could trigger acute metabolic decompensation with a high risk of worsening the outcome and even threatening the life of the patient.

We describe the nutritional and pharmacological management of a 2-year-old girl with a severe form of PA and genitourinary embryonal RMS, in whom a multimodal treatment approach was used.

Case Report

The patient was a 23-month-old girl who was born at term after an uncomplicated pregnancy and delivery. She presented at 22 days of life with severe encephalopathy, metabolic acidosis and hyperammonemia (900 μmol/L) that required hemodiafiltration 24 h and respiratory support for 9 days. She was diagnosed with PA based on urine organic acids and acylcarnitines profile. She was found to be homozygous for the V681_A706del26 (c.2041-2924del3889) mutation in the *PCCA* gene; this is a severe mutation which leads to exon 23 skipping (Desviat et al. 2009; Kraus et al. 2012). A gastrostomy was implemented at 5 months because of feeding problems. During the first 2 years of life she had a mild developmental delay and a good nutritional status in spite of very low natural protein tolerance (9 g/day at 2 years). She was fed through gastrostomy with a normocaloric hypoproteic diet supplemented with a propiogenic-free amino acid-based formula. She was allowed also had small amounts of vegetables and fruits. L-carnitine (100 mg/kg/day) and L-isoleucine (300 mg/day) were also supplemented to prevent deficiency.

At 23 months of age, after several vaginal bleeding episodes and the observation of a polypoid mass protruding from the vagina, an examination under anesthesia was performed. Biopsies of the vaginal mass and urinary bladder revealed the presence of an embryonal rhabdomyosarcoma affecting the vagina and urinary bladder. A magnetic resonance imaging (MRI) scan, a bone marrow aspirate, a bone scintigraphy and a chest computed tomography were then performed to assess the extent of spread of the tumor, after which the tumor was classified as standard risk group, subgroup D, using the European Pediatric Soft Tissue Sarcoma Study Group (EPSSG) classification for nonmetastatic RMS. Oncologists recommended treatment with conservative surgery, nine cycles of chemotherapy with iphosphamide, vincristine and actinomycin (IVA) every 20 days, and brachytherapy. Due to the possibility that the child could present decompensations related either to infections, fasting or side effects of chemotherapy, we elaborated three different courses of treatment (Table 1): treatment 1, when the patient was stable, at home or in the hospital, intermittent enteral feeding through gastrostomy was maintained. This diet was

Table 1 Nutritional and pharmacological management during stable days (treatment 1), chemotherapy days (treatment 2) and in case of decompensation (treatment 3)

	Treatment 1	Treatment 2	Treatment 3
Feeding regimen	Bolus/ continuous[a]	CEF[b]	CEF[b]
Energy (kcal/kg/day)	70	70	77
NP (g/kg/day)	0.6	0.3	0
Protein equivalent (g/kg/day)	0.8	0.8	0.8
TP (g/kg/day)	1.4	1.1	0.8
Isoleucine (mg/day)[c]	300–350	–	–
Carnitine (mg/kg/day)	100	150	150
N-Carbamylglutamate (mg/kg/day)	–	100	100

NP Natural protein, *TP* Total protein, *CEF* Continuous enteral feeding

[a] Bolus feeding during the day and continuous feeding overnight

[b] CEF over 24 h

[c] On the first and the second cycles de dose of isoleucine was 300 mg/day and since the third cycle was 350 mg/day

designed according to the recommendations for children with her age and sex (Trumbo et al. 2002; Dewey et al. 1996) but adapted to the protein tolerance and energy expenditure of the patient in the previous months; treatment 2 was recommended during the days she received chemotherapy: it consisted on the same energy intake, half of natural protein and the same amount of amino acid-based formula. When on this regimen we used continuous feeding through gastrostomy tube, over 24 h, in order to prevent vomiting and ensure the intake. Treatment 3 was designed in case a decompensation occurred; it consisted on 10% more energy and had no natural protein but keeping amino acid-based formula. In order to provide the quantities of different nutrients according to the recommendations, we used a mixture of infant formula milk as natural protein source, amino acid-based formula omitting the propiogenic ones and a free-protein formula. Furthermore we supplemented with 300 mg of isoleucine during the stable days. L-carnitine was given at 100 mg/kg/day on stable days and at 150 mg/kg/day during chemotherapy days. N-carbamylglutamate (NCG) was administered at 100 mg/kg/day the days of chemotherapy to prevent hyperammonaemia (Table 1).

Ammonia, bicarbonate, protein, albumin, liver function tests, renal function tests and ketonuria were determined before and during chemotherapy days, and also when clinically indicated. Amino acids, organic acids, acylcarnitines and OLCFA were determined before chemotherapy and in cycles 5th and 9th. Nutritional status was assessed by weight, height and BMI z-score (Hernández et al. 2002) and other biochemical parameters determined in cycle 9.

None of the nine cycles of chemotherapy had to be stopped or postponed; therefore the patient received every cycle at the precise moment. In Table 2 the side effects of chemotherapy she presented are shown, as well as her biochemical parameters. Throughout the 7 months with chemotherapy no decompensation episodes were observed, but she had to be fully tube-fed because of food refusal. She had no problems with her gastrostomy. The patient had three bacteriemias related to *Staphylococcus Epidermidis* porth-a-cath® infections and during these episodes, ketosis was present and, in two of them, also a mild hyperammonaemia (maximum levels of 119 and 100 μmol/L). Bicarbonate was always normal, as were medium levels of ammonia. OLCFA values were higher in cycles 5th and 9th than before chemotherapy. On the second cycle, isoleucine plasmatic levels were very low, so that we had to increase the dose to 350 mg/day since the third cycle. With reference to nutritional status, the weight, height and BMI z-score are shown in Table 3, and some of the biochemical parameters are shown in Table 4, all of which were within the normal ranges with exception of vitamin B12 and vitamin E, which were elevated in spite of not receiving any multivitamin supplements.

Discussion

Nutritional support in pediatric oncology patients, besides maintaining growth and development, may enhance therapy results, decrease complications, improve the immunological status of the child and hopefully improve their chances of survival. Additionally, in patients with PA nutritional therapy is the mainstay of long-term treatment (Ogier de Baulny et al. 2012; McDonald et al. 2007).

The aims of treatment in our patient were to avoid decompensations, which could either interrupt or delay chemotherapy, and to provide an adequate intake of energy, proteins, minerals, vitamins and essential fatty acids to promote growth. Protein requirements in patients with PA are not well established and even less in patients with PA and oncological disease; an excess of protein could precipitate decompensation but an over-restriction of protein could lead to poor growth and also to an endogenous protein catabolism putting the child at risk of metabolic decompensation. Because of that, amino acid-based formulas and additional energy sources are often needed to promote anabolism (Yannicelli 2006). The clinical value of amino acid-based formulas remains controversial and no long term controlled studies have been published; some studies have shown that amino acid supplement does not seem to have an important role in the nutritional and developmental outcome (Touati et al. 2006),

Table 2 Side effects of chemotherapy agents and values of ammonia, bicarbonate, protein, albumin, isoleucine, OLCFA and ketonuria previous to the diagnosis of RMS and during the nine cycles of chemotherapy

Cycles (days in ward)	Previous	1st (15 days)	2nd (11 days)	3rd (4 days)	4th (14 days)	5th (4 days)	6th (7 days)	7th (3 days)	8th (3 days)	9th (3 days)
Side effects of chemotheray	–	I, P, H	P	–	I, P, H	–	I, P	–	–	–
Ammonia[a] (<50 μmol/L)	63	**119**	50	32	**100**	65	46	44	58	45
		38	30	31	54	30	30	31	44	37
Bicarbonate (23-27 mmol/L)	22.2	21.35	25	24	23.6	22	26	23	23	24
Ketonuria	(–)	++	–/++	(–)	++/–	+	+++	(–)	(–)	(–)
Protein (6.4–8.3 g/L)	6.3	6.2	6.1	6.2	6.6	6	**5.6**	6.6	6.2	5.8
Albumin (3.5–5 g/L)	4.3	3.8	3.8	4.5	4.7	4.3	4	4.4	4.5	4.3
Isoleucine (30–65 μmol/L)	44	–	**11**	–	–	**20.4**	–	–	–	**14**
OLCFA (0.31–0.75%)	0.72	–	–	–	–	2.45	–	–	–	1.75

Ammonia and bicarbonate were determined in plasma and the rest of biochemical parameters were determined in serum

I Infection, *P* Pancitopenia, *H* Hypertransaminasaemia, *RMS* Rhabdomyosarcoma, *OLCFA* Odd-numbered long-chain fatty acids

Values in bold are out of the normal range

[a] In the top row are maximum values of ammonia and in the bottom row the medium ones

Table 3 Growth through chemotherapy

	Before CT	During CT	After CT
Age (months)	24	27	31
Weight (z-score)	13.40 kg (1.31)	14.75 kg	16.60 kg (2.02)
Height (z-score)	84.5 cm (–0.31)	87.5 cm	91 cm (0.41)
BMI (z-score)	18.77 (1.53)	19.27	20.05 (2.52)

CT Chemotherapy

Table 4 Biochemical parameters at the end of chemotherapy (9th cycle)

	Patient	Normal values
Prealbumin (mg/dL)	27	14–40
RBP (mg/dL)	4.31	2.80–6.30
Folic Acid (ng/mL)	14.55	2.60–18.70
Vitamin B12 (pg/mL)	>2,000	200–753
Vitamin A (μmol/L)	2.01	1.10–2.80
Vitamin E (μmol/L)	40.50	8.40–24
Vitamin D (ng/mL)	36	17–58
Zinc (μg/mL)	70	60–100
Docosahexaenoic acid (μmol/L)	220.7	110–513
Arachidonic acid (μmol/L)	596	447–898

RPB Retinol-binding protein

whereas others have reported improved growth and nutritional status of children using these formulas (Yannicelli et al. 2003). Our patient had a very low natural protein tolerance, therefore, these formulas allowed us to meet requirements for normal growth.

During infections or other situations in which there is low intake, patients with PA are at risk of developing metabolic acidosis and encephalopathy. Chemotherapy treatment usually entails reduced appetite and frequent vomiting, so we considered chemotherapy-days as a risk for decompensation in our patient and decided to implement a preventive dietary regimen for those days. What we did was to reduce natural protein by half, but maintaining the same amino acid-based formula and energy supplements. In our patient, feeding through the gastrostomy was essential to provide an adequate intake. Whereas gastrostomy feeding has become the main method of providing long term nutritional support in other areas of pediatrics, until recently it has not been commonly used in children with oncological diseases because of the perceived risk of infectious complications. In our case it has proven to be a safe and effective method of nutritional support.

Hyperammonaemia is a complication of PA, due to an inhibition of N-acetylglutamate synthase (NAGS) for the propionyl CoA accumulated. It is a true emergency, with high mortality and neurological complications in most of survivors, which should be treated promptly. Gebhardt et al. described two patients with PA and hyperammonaemia who were treated with N-carbamylglutamate (NCG), an analog of N-acetylglutamate. Their blood ammonia levels were decreased even by first dose of NCG and normalized in a 6-h period (Gebhardt et al. 2005). Since then, other cases of hyperammonaemia secondary to PA treated with NCG have

been published (Filippi et al. 2010; Jones et al. 2008; Schwahn et al. 2010) and it has been showed that NCG reduces plasma levels of ammonia and glutamine and increases the rate of ureagenesis in patients with PA (Ah Mew et al. 2010). We treated our patient with NCG during the days of chemotherapy in order to prevent hyperammonaemia owing these days she could decompensate by vomiting. In our knowledge NCG has never been used to prevent hyperammonaemia in patients with PA.

In summary, with an adaptation of her nutritional and pharmacological treatment, our patient tolerated chemotherapy well, as maintained a good nutritional status. Continuous feeding through gastrostomy, the use of amino acid-based formulas, and preventive treatment with NCG during the days chemotherapy was administered are the principal measures we propose in these situations.

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Details of the Contribution of Individual Authors

Martín-Hernández E, Quijada Fraile P and García-Silva MT are the specialists in metabolic diseases in charge of the patient. They participated in the conception and design of the study.

Oliveros Leal L, is the dietician in charge of nutritional management of the patient. She participated in the conception and design of the study.

Baro M, Pérez-Alonso V and Vivanco JL are the oncologists in charge of the patient. They participated in the conception and design of the article.

Pérez-Cerdá C, specialist in biochemistry, has provided scientific data for the present manuscript.

Martín-Hernández E has written the article

All of them have critically read the contents of the manuscript

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Competing Interests

All authors declare that the answer to all questions on the JIMD competing interest are "No", and therefore they have nothing to declare

Ethics approval was not required

Consent for publication was obtained from the parents of the patient

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