Dietary Therapy in a Girl with Propionic Acidemia: Supplement with Leucine Resulted in Catch Up Growth

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SATOH, T., NARISAWA, K., TAZAWA, Y., SUZUKI, H., HAYASAKA, K., TADA, K. and KAWAKAMI, T. *Dietary Therapy in a Girl with Propionic Acidemia: Supplement with Leucine Resulted in Catch Up Growth.* Tohoku J. exp. Med., 1983, **139** (4), 411-415 — A 15-month-old girl with propionic acidemia presented a failure to thrive and muscular hypotonia, who had been treated with diets low in leucine, valine, isoleucine, threonine and methionine. Supplementation with leucine gave her a catch up growth and brought about an improvement in muscular hypotonia in parallel with restoration of plasma leucine which had been below normal range during the treatment with the above diets. Oral loading test of leucine produced no ketoacidosis. These findings indicate that the restriction of leucine is not necessary in the dietary management of propionic acidemia. ——— propionic acidemia; restriction of leucine; leucine deficiency; supplement with leucine; catch up growth

Propionic acidemia is an inborn error of metabolism in which large amounts of propionic acid are found in blood and urine. Valine, isoleucine, threonine and methionine are the major precursors of propionic acid. It is known that ketoacidosis develops as a result of loading with excessive amounts of these amino acids (Childs et al. 1961). Also leucine is known to be noxious to the patient with propionic acidemia (Childs et al. 1961), although the amino acid is not metabolized to propionyl-CoA in man. Based on the above finding, in a dietary management of the disease, a diet low in not only valine, isoleucine, threonine and methionine, but also leucine has been devised and recommended (Nyhan 1967; Brandt et al. 1974). Recently, we treated a girl with propionic acidemia who had failed to thrive on diets low in these five amino acids and showed a catch up growth by supplement with leucine.

CASE REPORT

C.A., a girl, aged 15 months, was referred to our hospital because of failure to thrive. She was born after uneventful pregnancy and delivery, weighing 3,190 g.

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Since three days of life, she had frequent episodes of vomiting and lethargy. Gas chromatographic analysis showed an increase in propionic acid in serum and urine. Liver specimen was biopsied for enzymatic diagnosis and a defect of propionyl-CoA carboxylase was demonstrated as described in our previous report (Hayasaka et al. 1982). Since 65th day of age, she was put on a low protein diet (0.8 g/kg/day) supplemented with synthetic amino acid mixture devoid of leucine, valine, isoleucine, threonine and methionine (Meiji 8001, Meiji Milk Company, Tokyo). On this regimen, the frequency of acidotic attacks was decreased, however, her gain in body weight was poor. On admission, her physical examination revealed a small (body weight: 7.4 kg) and floppy infant. She lay with her legs in a frog position. She could not sit straight up.

MATERIALS AND METHODS

Formula low in protein was supplemented with two kinds of synthetic amino acid mixture devoid of valine, isoleucine, threonine and methionine. One does not contain leucine (Meiji 8001, Meiji Milk Company, Tokyo. Contents per 100 g powder containing 14.5% of synthetic amino acid mixture: phenylalanine 800 mg, lysine 1,920 mg, tryptophan 980 mg, histidine 720 mg, arginine 1,280 mg, glutamic acid 2,560 mg, proline 1,040 mg, serine 800 mg, alanine 1,200 mg, tyrosine 720 mg, aspartic acid, 1,280 mg, cystine 720 mg and glycine 480 mg). The other contains leucine (S-22, Snow Brand Milk Company, Tokyo. Contents per 100 g powder containing 12% of synthetic amino acid mixture: leucine 1,160 mg, phenylalanine 613 mg, lysine 1,531 mg, tryptophan 296 mg, histidine 510 mg, arginine 980 mg, glutamic acid 1,990 mg, proline 1,020 mg, serine 717 mg, alanine 1,020 mg, tyrosine 513 mg, aspartic acid 1,020 mg and cystine 530 mg). These mixtures were supplemented with iron, calcium, magnesium, zinc, copper and a multiple vitamin preparation.

Extraction and quantification of propionic acid in plasma were performed according to the methods described by Sasaki et al. (1969) and Perry et al. (1970), respectively. Plasma amino acids were analysed on a automatic amino acid analyser (Hitachi Model 835). Urine ketones were qualified by ketostix (Ames Division Miles-Sankyo Co., Ltd.).

RESULTS

On admission, dietary therapy was designed to provide low protein diets (1.2 to 0.6 g/kg/day) (Formulas No. 1, No. 2, No. 3) with addition of the synthetic amino acid mixture devoid of leucine, valine, isoleucine, threonine and methionine (Meiji 8001, 1.0 to 1.5 kg/kg/day) (Table 1). On the regimen containing 1.0 to 1.2 g/kg of protein (Formulas No. 1, No. 2), her appetite tended to decrease and sometimes she actually took 50% to 75% of protein prescribed. During on Formula No. 2, ketoacidosis developed with increase in plasma propionic acid (8.5 mg/100 ml). The administration of biotin (100 mg daily) was found to be without effect. Clinically, her gain in body weight was poor (Fig. 1) even while she was free of acidosis. Her muscles remained hypotonic and motor development was retarded. We thought the amount of protein to be too much for this child. So protein intake was reduced to 0.6 g/kg daily (Formula No. 3). On this regimen, the level of plasma propionic acid was decreased to a lower level (0.16–0.26 mg/100 ml) and she showed no acidosis, however, her gain in weight remained poor (below 10 percentile of

TABLE 1. *Composition of the experimental formulas*

Formula	No. 1	No. 2	No. 3	No. 4			
Protein (g)	1.0	1.2	0.6	0.8			
Amino acid mixture (g)				a	b	c	d
Meiji 8001	1.0	1.0	1.5	1.0	0.8	0.45	—
S-22	—	—	—	0.4	0.6	0.85	1.1
Calories (kcal)	100 to 125	120	120	110			
Contents of essential amino acids of the formulas (mg)							
Valine	54	65	33	44	44	44	44
Isoleucine	48	58	29	38	38	38	38
Threonine	42	50	25	33	33	33	33
Methionine	20	24	12	16	16	16	16
Leucine	92	110	55	116	133	157	179
Lysine	198	212	239	237	236	223	194
Phenylalanine	100	109	110	112	111	104	92
Tryptophan	80	83	109	88	79	62	37

All values are in per kg body weight per day.

Amino acid mixture is not included in the calculation of protein content of the formulas.

Fig. 1. Growth curve in body weight compared with 10th and 90th percentile curves of normal Japanese female infants. Note a catch up growth and a rise in plasma leucine into a normal range in response to increase in leucine intake.

*Plasma propionic acid was increased to 8.5 mg/100 ml and ketoacidosis developed (see text).

weight compared with normal Japanese female infant) (Fig. 1). During on these formulas (Formulas No. 1, No. 2, No. 3), the concentration of leucine in plasma remained below normal range [0.28–0.59 mg/100 ml (normal: 0.66–2.60 mg/100 ml)] (Fig. 1), whereas those of valine, isoleucine and threonine were kept within normal range or above normal levels. [valine 1.78–4.50 mg/100 ml (normal: 1.50–3.74 mg/100 ml), isoleucine 1.19–1.79 mg/100 ml (normal: 0.32–1.44), threonine 1.98–2.41 mg/100 ml (normal: 0.78–1.82 mg/100 ml)]. Such a pattern of plasma aminogram is similar to that seen in leucine deficiency (Snyderman et al. 1961). Therefore, to increase her leucine intake, the amino acid mixture (Meiji 8001) was gradually replaced with leucine containing mixture (S-22) under a protein intake of 0.8 g/kg daily (Formulas No. 4 a, b, c and d). Then she began to thrive immediately and showed a catch up growth in parallel with restoration of leucine (Fig. 1) accompanied with normalization of valine, isoleucine and threonine in plasma. During the period on this regimen, she was free of acidosis except when she had a respiratory infection. Also, she showed an improvement of muscular hypotonia and began to crawl about on all fours. Three months after the initiation on the

Fig. 2. Changes in plasma bicarbonate, plasma propionic acid, plasma leucine and urinary ketones in response to the loading of leucine (220 mg/kg). Note no significant change in plasma bicarbonate or plasma propionic acid. Urinary ketone was negative (ketostix) during this experiment. *Negative.

regimen supplemented with leucine, she could walk with support. By seven months on the diet, she became possible to stand alone and walk without support. DQ, which had been 65 at 18 months of age, was found to be 78 at the age of 25 months. A loading of large amount of leucine (220 mg/kg orally) produced neither ketoacidosis nor an increase in propionic acid in plasma (Fig. 2).

DISCUSSION

Leucine is one of the essential amino acids and the amount of its daily requirement in infancy is considered to be larger than other amino acids (Holt 1968). However, it was reported that leucine was one of the amino acids noxious to a child with propionic acidemia (Childs et al. 1961) and in a dietary management, a diet restricted of not only amino acids which are in vivo convertible to propionyl-CoA but also leucine was devised (Nyhan 1967; Brandt et al. 1974). Our patient demonstrated that increase in leucine intake brought about a catch up growth and an improvement in muscular hypotonia and motor development, accompanied with restoration of plasma leucine which had been below normal range during on diets low in leucine (Formulas No. 1, No. 2 and No. 3). It seemed that she had been deficient in leucine intake on the diets restricted in leucine, valine, isoleucine, threonine and methionine. Moreover, a loading of large amount of leucine produced no ketoacidosis. These findings indicate that the restriction of leucine is not necessary in the dietary management of propionic acidemia.

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