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Nutritional status of patients with phenylketonuria in Japan

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ABSTRACT

Accumulating evidence suggests that hyperphenylalaninemia in phenylketonuria (PKU) can cause neuropsychological and psychosocial problems in diet-off adult patients, and that such symptoms improve after resumption of phenylalanine-restricted diet, indicating the need for lifetime low-phenylalanine diet. While limiting protein intake, dietary therapy should provide adequate daily intake of energy, carbohydrates, fat, vitamins, and microelements. We evaluated nutrient balance in 14 patients with classical PKU aged 4–38 years. Approximately 80–85% of the recommended dietary allowance (RDA) of protein in Japanese was supplied through phenylalanine-free (Phe-free) milk and Phe-free amino acid substitutes. Nutritional evaluation showed that the calorie and protein intakes were equivalent to the RDA. Phenylalanine intake was 9.8 ± 2.2 mg/kg of body weight/day, which maintained normal blood phenylalanine concentration by the 80% Phe-free protein rule. The protein, fat, and carbohydrate ratio was 9.5:23.9:66.6% with relative carbohydrate excess. Phe-free milk and amino acid substitutes provided 33.7% of carbohydrate, 82.1% of protein, and 66.7% of fat intake in all. Selenium and biotin intakes were 25.0% and 18.1% of the RDA and adequate intake (AI) for Japanese, respectively; both were not included in Phe-free milk. PKU patients showed low serum selenium, low urinary biotin, and high urinary 3-hydroxyisovaleric acid in this study. The intakes of magnesium, zinc, and iodine were low (71.5%, 79.5%, and 71.0% of the RDA, respectively) and that of phosphorus was 79.7% of the AI, although they were supplemented in Phe-free milk. PKU patients depend on Phe-free milk and substitutes for daily requirement of microelements and vitamins as well as protein and fat. Development of low-protein food makes it possible to achieve the aimed phenylalanine blood level, but this lowers the intake of microelements and vitamins from natural foods. The dietary habits vary continuously with age and environment in PKU patients. We recommend the addition of selenium and biotin to Phe-free milk in Japan and the need to review the composition of microelements and vitamins in A-1 and MP-11 preparations.

1. Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficiency in hepatic phenylalanine hydroxylase and is usually diagnosed early in life. Unless the affected child is maintained on a strict low-phenylalanine diet, PKU leads to mental retardation, seizures, behavioral difficulties, and other neurological symptoms [1]. The introduction of newborn mass screening for this disorder allowed early diagnosis of PKU, increased the chance of normal development of affected infants through early-intervention dietary treatment, and markedly improved long-term prognosis. At first, restriction of phenylalanine intake was thought to be necessary for brain development in infants and children with PKU. The initial protocol did not state the low-phenylalanine diet prescribed for classical PKU in the second decade of life. However, accumulating evidence in the last several years suggested that hyperphenylalaninemia can cause neuropsychological and psychosocial problems in diet-off adults, and that such symptoms improved after resumption of phenylalanine-restricted diet [2–5]. Thus, diet therapy is necessary and important over the lifetime of patients with PKU.

The dietary therapy for PKU includes restriction of intake of natural foods, such as high protein, but at the same provides protein at amounts

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similar to those consumed by age- and sex-matched healthy subjects, using phenylalanine-free (Phe-free) protein substitutes to maintain blood phenylalanine concentration within the therapeutic range. Furthermore, it is important that the daily intake includes the same amount of energy and balanced diet of carbohydrate, fat and protein, similar to sex- and age-matched healthy individuals. Therefore, Phe-free milk, A-1, MP-11, and low-protein rice, noodle, and bread are used for dietary therapy of PKU.

Phe-free milk, A-1 (a Phe-free amino acid substitute) and MP-11 (a low Phe peptide substitute) are available in Japan. The Phe-free milk is used with breast milk or general formula milk during the newborn period. It was approved for use as a medical product in 1980, and is supplied as a pharmaceutical product by Snow Brand Meg Milk Co., Ltd. (Tokyo). A-1 was developed by Snow Brand Meg Milk in 1981, and is comprised mainly of the same amino acids of Phe-free milk but does not contain fat, carbohydrates, microelements, or vitamins. On the other hand, MP-11 was developed in 1998 by Morinaga Milk Industry Co., Ltd. (Tokyo), and based on the nutritional requirements of PKU patients at that time; the product contains high concentrations of microelements but not vitamins [6]. MP-11 contains 280 mg of phenylalanine per 100 g. MP-11 consists of the amino acids dimers, and thus its digestion and absorption are better than the mixture of amino acid substitutes without the smell of amino acids. Patients can obtain A-1 and/or MP-11 through the Special Milk Safety Development Committee free of charge as social contribution from the companies and government subsidies.

Even if PKU patients have been detected in the newborn mass screening, patients with high blood phenylalanine concentration showed low IQ. Moreover, previous studies showed a negative correlation between blood phenylalanine concentration and IQ [7]. Magnetic resonance imaging (MRI) and electroencephalographic (EEG) findings indicate the need to maintain blood phenylalanine concentration below 480 μmol/L [8,9]. Blood phenylalanine concentration (>600 μmol/L) are reported to be associated with oxidative stress state in human [10]. Therefore, recent recommendations impose more strict limitation on phenylalanine intake in adults to maintain low phenylalanine concentration, compared with previous recommendations. At present, a threshold value of 600 μmol/L or less is set in many countries as the upper limit for blood phenylalanine concentration for patients aged ≥16 years [11]. The first Japanese guideline published in 1977 did not place a cap on blood phenylalanine concentration in adult patients with PKU. However, the second 1995 guidelines limited blood phenylalanine in such patients within the range of 180 to 900 μmol/L. On the other hand, the most recent Japanese guidelines in 2012 set the preferred blood phenylalanine concentration in adult PKU patients between 120 and 600 μmol/L.

Various types of low protein diet products (rice, noodles, bread) have been recently developed for patients with renal diseases. The development of low-protein rice (1/5–1/30 protein of normal rice) of good flavor has made it easier for PKU patients to maintain blood phenylalanine within the above range. This is particularly important for Japanese patients since boiled rice is the staple food in Japan. Strict limitation of consumption of natural protein may be associated with low intake of microelements and vitamins that are only present in natural protein. In addition, the Ministry of Health, Labour and Welfare has prohibited to supplement with biotin, selenium, and carnitine to formula milk including Phe-free milk and Phe-free amino acid substitutes. Biotin was permitted recently. Thus, the use of only these preparations could potentially lead to deficiency of microelements and vitamins. Thus far, there are hardly any reports on nutritional assessment of PKU patients in Japan, though zinc, selenium, iron, and vitamin B_{12} deficiency have been reported in PKU patients living in other countries [12–15].

In the present report, we demonstrate that 80 to 85% of daily protein intake should be from Phe-free milk, A-1, and MP-11 in PKU patients. We evaluate the nutritional intake, including those of the three major nutrients, microelements, and vitamins, in Japanese patients with PKU. We also report preliminary results of serum selenium, serum biotin, urinary biotin, and urinary 3-hydroxyisovaleric acid (3HIA).

2. Methods

2.1. Subjects

Nutritional evaluation was conducted in 14 patients (nine males) with classical PKU aged 4 to 38 years. All patients showed >1200 μmol/L of phenylalanine without dietary treatment and had severe phenotypic mutations in both alleles. In the dietary therapy of these PKU patients, 80–85% of age- and gender-specific recommended dietary allowance (RDA) for protein according to the Dietary Reference Intakes for Japanese 2010 [16] was taken from the Phe-free protein comprising Phe-free milk with/without Phe-free amino acid powder (A-1), and low phenylalanine peptide powder (MP-11). The natural protein taken is within 15–20% of the RDA. PKU patients generally consumed natural low-protein food and rice, noodle, and bread that have been improved to a low protein content. We have regulated the dietary food, protein restriction, and Phe-free materials in PKU patient according to the blood phenylalanine value and nutritional assessment. Table 1 lists the composition of Phe-free milk, A-1, and MP-11.

2.2. Nutritional evaluation

In the Dietary Reference Intakes for Japanese 2010, the “Estimated average requirement (EAR)” represents the estimated daily intake required by 50% of the population. Furthermore, the RDA means the estimated daily intake by 97–98% of the Japanese population, with a probability of lack of 2.5%. When the EAR and the RDA cannot be used based on scientific grounds, the “adequate intake (AI)” is set as the sufficient amount to maintain constant nutritional status, which is, in general, larger than the RDA. The “Tolerable upper intake level (UL)” is the

Table 1
Nutritive composition of Phe-free milk and medical amino acid substitutions for PKU patients in Japan.

	Phe-free milk	Phe-free amino acid powder (A-1)	Low Phe peptide powder (MP-11)
Protein (g)	15.8	93.7	75
Fat (g)	17.1	0	0
Carbohydrate (g)	60.4	0	7.2
Ash content (g)	3.68	2.9	7.4
Water substance (g)	2.97	3.4	2.8
Energy (kcal)	458	375	329
Phe (mg)	0	0	280
Ca (mg)	360	0	1100
Mg (mg)	34	0	300
Na (mg)	168	880	620
K (mg)	440	0	1400
P (mg)	270	0	600
Cl (mg)	320	1900	300
Fe (mg)	6	0	15
Zn (mg)	2.5	0	20
Cu (μg)	280	0	1000
I (μg)	25	0	150
Se (μg)	1	2	11
Vit A (IU)	1500	0	0
Vit B1 (mg)	0.36	0	0
Vit B2 (mg)	0.6	0	0
Vit B6 (mg)	0.4	0	0
Vit B12	1	0	0
Vit C (mg)	48	0	0
Vit D (IU)	300	0	0
Vit E (mg)	4.38	0	0
Ca pantothenate (mg)	2	0	0
Niacin (mg)	5	0	0
Folate (mg)	0.1	0	0
Choline (mg)	50	0	0
Biotin (μg)	0	0	0.6