Born at 27 weeks of gestation with classical PKU: challenges of dietetic management in a very preterm infant

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Abstract

Few cases of premature infants with classical phenylketonuria (PKU) have been reported. Treatment of these patients is challenging due to the lack of a phenylalanine (Phe)-free amino acid (AA) solution for parenteral nutrition. A boy born at 27 weeks of gestation with a weight of 1000 g was diagnosed with classical PKU on day 7 because of highly elevated Phe level at newborn screening (2800 μmol/L). Phe intake was suspended for 5 days and during this time intravenous glucose and lipids as well as small amounts of Phe-free formula through nasogastric tube were given. Because of insufficient weight gain attributable to deficiency of essential AA, a Phe-reduced, BCAA-enriched parenteral nutrition was added to satisfy AA requirements without overloading in Phe. Under this regimen, the boy started to gain weight, Phe plasma levels progressively reduced and normalized on day 19. At the age of 40 months, the patient shows normal growth parameters (height 25th percentile, weight 25-50th percentile, head circumference 50th percentile) with a normal result for formally tested psychomotor development (WPPSI-III). The good outcome of the patient in spite of over 2 weeks of extremely high Phe concentrations suggests that the premature brain may still have enough plasticity to recover. Lacking a Phe-free intravenous AA solution, successful management of premature infants with PKU depends on the child's tolerance of enteral nutrition. Although the coincidence of PKU and prematurity is rare, there is strong need for the development of an appropriate Phe-free amino acid solution for parenteral nutrition especially in case of gastro-intestinal complications of prematurity.

Introduction

Phenylketonuria (PKU; OMIM #261600) is an autosomal recessive inherited defect of phenylalanine hydroxylase (PAH, OMIM *612349, EC 1.14.16.1). PAH hydroxylates phenylalanine (Phe) to tyrosine (Tyr) in the presence of molecular oxygen and catalytic amounts of tetrahydrobiopterin (BH4), its essential cofactor. The PAH gene is located on chromosome 12q24.1 and a high number of allelic variants are known (www.biopku.org). PKU has an overall incidence in Europe and the USA of approximately 1:10,000-20,000 live births.[1] If left untreated, PKU results in elevated blood Phe concentrations, low-to-normal blood Tyr concentrations and severe mental retardation with an intelligence quotient (IQ) between 30 and 50.[2] Reduced cerebral monoaminergic neurotransmitters and reduced protein synthesis, caused by impaired brain uptake of non-Phe large neutral amino acids in the presence of elevated plasma Phe concentrations seem to be the main pathophysiologic mechanism in PKU.[3] The aim of the treatment is to reduce the plasma Phe concentration sufficiently to prevent neurological impairment. Plasma Phe concentration results from residual PAH activity, nutritional Phe intake and growth rate. Depending on the residual enzyme activity a more or less strict reduction of dietary Phe intake is necessary to achieve the desired plasma Phe concentration. Complementation with a Phe-free amino acid mixture is necessary in the majority of patients to prevent protein deprivation and assure normal growth. Furthermore, there is a whole range of low-protein food available to replace protein-rich dietary components.[2] In classical PKU this treatment is very restrictive and may be associated with a risk of nutritional deficiencies. During intercurrent illness a high-energy intake is necessary to counteract catabolism of body protein leading to higher plasma Phe levels. Sick children are often unable to take their prescribed diet and need calory administration via naso-gastric tube or intravenously. The treatment of premature PKU patients is very difficult as there are neither data about daily Phe requirements nor specialized products for this age group. Promotion of anabolism (energy requirement for growing premature infants: 110-130 kcal/kg/d) seems to be the best rational to stabilize plasma Phe levels. National guidelines of several European countries for the management of PKU recommend that treatment should start as early as possible after birth and should be monitored by Phe concentrations in blood and clinical parameters.[4-6] It is known that the developing brain is most sensitive to Phe toxicity, In 2000 Burgard showed that the IQ decreased by 0.5 standard deviation (approximately 7 points) for each 300 μmol/L rise in blood Phe level. IQ scores appeared to stabilize after the age of 10 years, even when Phe levels exceeded 1200 μmol/L, suggesting that diet could be somewhat relaxed in adolescence.[7] Indeed, until recently, diet was stopped in many countries after the age of 12 years. In a longitudinal collaborative study Koch et al reported that early-treated adults who continued diet had higher IQs than adults who discontinued diet at an early age. In addition, adults with PKU who continued diet performed at a level comparable to genetic expectations as measured by their parents' IQ.[8] High Phe levels are known to be toxic for the fetal brain, as the main consequences of maternal PKU are microcephaly and mental retardation.[9] However, no clear data are available about the effect of high Phe in the brain of premature babies and especially about blood threshold Phe concentrations and/or duration of high Phe levels on clinical outcome of these patients. There are only few reports of preterm infants with PKU in the literature.[10-13] Here we report on our experience in the management of a very preterm infant with classical PKU.

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Case Report

The boy is the first child of non-consanguineous parents of Swiss origin. In the 26th

week of gestation the mother was diagnosed to have severe arterial hypertension and vaginal bleedings. In the 27th week premature uterine contractions were noticed. The mother received a tocolysis, but due to a placental abruption the patient was born at 27 weeks of gestation after antenatal pulmonary maturation with corticosteroids (2×12 mg of betamethasone intramuscularly with an interval of 24 h). His growth parameters were appropriate with a birth weight of 1000 g (10th percentile), a length of 38 cm (50-90th percentile) and a head circumference of 26 cm (50-90th percentile). Neonatal adaptation was good for his gestational age. Due to a wet-lung syndrome he needed respiratory support with continuous positive airway pressure (CPAP) for a few days. He was diagnosed with classical PKU (genotype c.1066-11G>A/c.1315+1G>A) due to highly elevated phenylalanine (Phe) level at newborn screening (2800 μmol/L), performed on day 4. On day 7, when newborn screening results were available, plasma Phe level was 3696 μmol/L. At this time the boy received little amounts of enteral nutrition (Beba Alprem 16%, 60 ml/kg in 12 feeds) completed with a parenteral nutrition (Vaminolact®, glucose and lipids) leading to a protein intake of 3.9 g/kg/day (Figure 1 and Table 1). The rather high protein intake for weight and age probably explains the very high plasma Phe level in this patient. Due to the diagnosis of PKU Phe intake was arrested for 5 days (Figure 2 and Table 1). During this time the boy received intravenous glucose and lipids as well as – due to the lack of a Phe-free

Table 1. Nutritional intake during the first 35 days of life: Detailed information about total calorie intake (kcal/kg/d), parenteral calorie intake (kcal/kg/d), enteral calorie intake (kcal/kg/d), total protein intake (g/kg/d), parenteral protein intake (g/kg/d), enteral protein intake, body weight (kg), phenylalanine (Phe) intake (mg/d and mg/kg/d) and Phe and tyrosine (Tyr) concentrations in plasma (mol/L).

Day	Body weight (kg)	Phe Plasma (μmol/L)	Tyr Plasma (μmol/L)	Phe intake (mg/d)	Phe intake (mg/kg/d)	Total protein intake (g/kg/d)	Enteral protein intake (g/kg/d)	Parenteral protein intake (g/kg/d)	Total calorie intake (kcal/kg/d)	Parenteral calorie intake (kcal/kg/d)	Enteral calorie intake (kcal/kg/d)
1	1	-	-	77	77	1	0	1	34	34	0
2	0.87	-	-	136	156	1.8	0.1	1.7	49	44	5
3	0.87	-	-	241	277	3.3	0.3	3	68	58	10
4	0.871	-	-	247	284	3.4	0.4	3	81	67	14
5	0.834	2840	-	252	302	3.6	0.6	3	78	59	19
6	0.872	-	-	259	297	3.8	0.8	3	93	66	27
7	0.915	3696	21	279	305	3.9	0.9	3	113	70	43
8	0.9	3403	67	0	0	0.9	0.9	0	90	45	45
9	0.9	2924	93	0	0	1.1	1.1	0	109	57	52
10	0.918	2993	132	0	0	1.3	1.3	0	110	49	61
11	0.9	2231	88	0	0	1.4	1.4	0	111	39	72
12	0.904	-	-	0	0	2.2	2.2	0	120	39	81
13	0.944	1467	123	11	12	3.4	2.4	1	121	31	90
14	0.97	-	-	3	3	3.1	2.8	0.3	125	22	103
15	0.98	830	48	3	3	3.4	3.1	0.3	136	22	114
16	0.967	-	-	0	0	3.3	3.3	0	120	0	120
17	0.986	-	-	0	0	3.3	3.3	0	120	0	120
18	1.009	34	58	32	32	3.4	3.4	0	123	0	123
19	1	-	-	32	32	3.4	3.4	0	123	0	123
20	1.025	17	52	32	31	3.4	3.4	0	123	0	123
21	1.025	-	-	102	100	3.9	3.9	0	137	0	137
22	1.03	-	-	102	99	3.9	3.9	0	137	0	137
23	1.05	-	-	102	97	3.9	3.9	0	137	0	137
24	1.11	-	-	102	92	3.9	3.9	0	137	0	137
25	1.13	16	19	171	151	4.1	4.1	0	142	0	142
26	1.145	-	-	171	149	4.1	4.1	0	142	0	142
27	1.185	-	-	171	144	4.1	4.1	0	142	0	142
28	1.147	251	26	120	105	3.8	3.8	0	134	0	134
29	1.283	-	-	120	94	3.3	3.3	0	117	0	117
30	1.335	-	-	120	90	3.3	3.3	0	117	0	117
31	1.34	-	-	120	90	3.3	3.3	0	117	0	117
32	1.32	-	-	120	91	3.3	3.3	0	117	0	117
33	1.39	127	214	120	86	3.5	3.5	0	125	0	125
34	1.39	-	-	120	86	3.5	3.5	0	125	0	125
35	1.4	-	-	120	86	3.5	3.5	0	125	0	125

intravenous amino acid solution - little amounts of Phe-free formula (65-92 mL/kg/day with a concentration of 14%, in 2-hourly feeds) through a nasogastric tube. However, because enteral feeding was poorly tolerated, the volume could not be increased rapidly. This led to poor weight gain and an only very slowly declining Phe level despite Phe deprivation (Table 1). In order to promote anabolism and thus induce protein synthesis and growth, a parenteral nutrition solution rich in branched-chain amino-acids, relatively poor in Phe and unfortunately lacking tyrosine, commonly used for hepatic insufficiency, was administered (Aminosteril® Hepa 8%). Under this regimen (Table 1), Phe plasma levels progressively diminished and finally normalized on day 18 when intake of natural protein (infant formula) was started. From day 19 to day 25 an oral supplementation with leucine (4×25 mg) and isoleucine (4×50 mg) was necessary to prevent depletion of these essential amino acids. The newborn lost a maximum of 16% of his birth weight, which was attained again on day 18. Parenteral nutrition was stopped on day 16 when the baby tolerated complete enteral nutrition (only Phe-free formula at a concentration of 15%). During several weeks we tried to find the balance between the high caloric and protein requirements, the limited tolerance of liquid administration, and the risk of necrotizing enterocolitis under concentrated enteral nutrition, all typical problems of premature children.

The patient always showed appropriate growth with height initially on the 10th percentile, going up to the 50th percentile at term and finally reaching the 25th percentile at at 40 months. Weight was initially on the 50th percentile going up to the 97th percentile at a corrected age of 3 to 6 months and finally stabilizing on the 50th percentile. Head circumference was initially on the 90th percentile and slowly came up to the 50th percentile by the corrected age of 18 months stabilizing there. He was seen for neurodevelopmental follow-up at the corrected ages of 6 months, 18 months, 24 months and at the chronological age of 40 months. Testing during the first 2 years was done with the Bayley Scales of Infant Development and with the French version of the WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence, third edition) at the age of 40 months. Standard neurological examination has remained normal. Formal developmental testing has shown scores in the normal range, with some behavioral issues in the last examination. He has a rather low Phe tolerance (~200 mg/d) but keeps a good metabolic control (average plasma Phe level 277 μmol/L during the first two years) on diet.

Discussion

The little reported experience shows that the management of classical PKU in preterm infants is not yet established. Adequate treatment of these patients is complicated by two problems: the lack of a Phe free amino acid solution for parenteral infusion, and the lack of reference values for safe Phe plasma concentrations related to gestational age.

Cole *et al*. published the case of a premature girl (second twin, less than 32 weeks of gestation) with a birth weight of 1480 g (Table 2). She was diagnosed with PKU on day 12 with an initial very high Phe level of 5670 μmol/L while

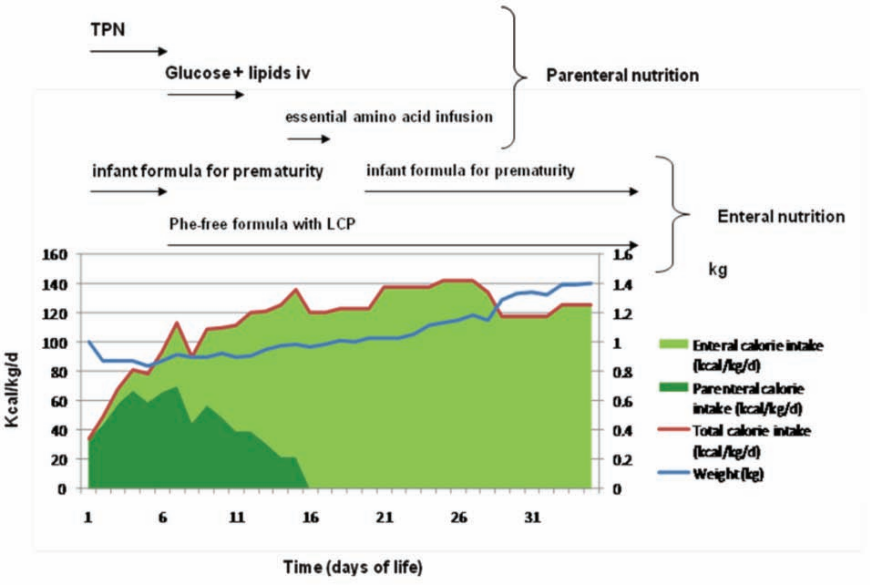

Figure 1. Evolution of parenteral and enteral nutrition during the first 35 days of life: the body weight (kg) is indicated by the blue curve, total calorie intake (kcal/kg/d) by the red curve. Proportions of parenteral (dark green) and oral (light green) nutrition are demonstrated. Start and duration of specific products is marked above the graphic.

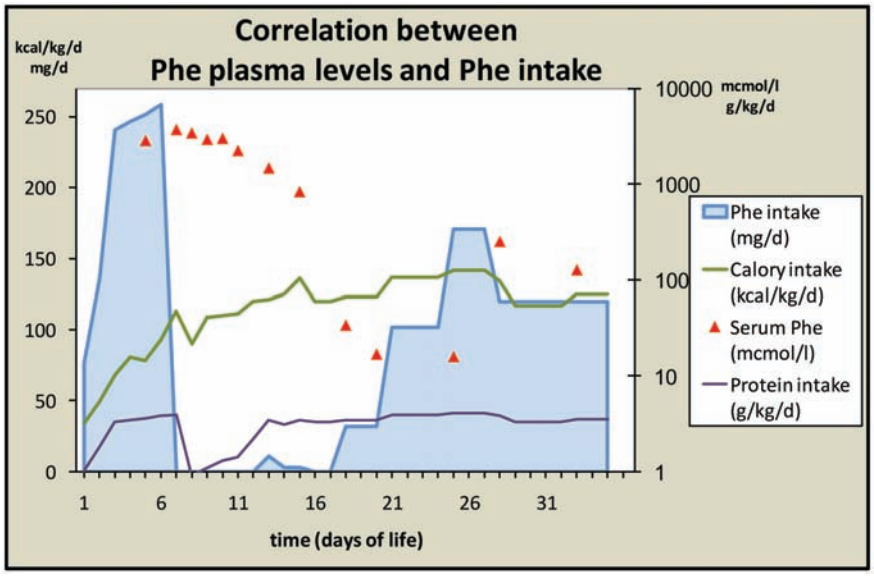

Figure 2. Correlation between phenylalanine plasma levels and phenylalanine intake during the first 35 days of life: Phenylalanine intake (mg/d) is given in light blue, total protein intake (g/kg/d) in dark blue, calorie intake in green and plasma phenylalanine levels in red triangles.

on parenteral nutrition for prematurity. At a few months of age she had a relatively high Phe tolerance of 97-128 mg/kg/d. Follow-up was reported until the age of 16 months with normal mental and motor development. The authors draw attention to the fact that Phe-free amino acid infusions might be necessary for preterm infants who require long-term treatment.[10] In 1985, Shortland et al. reported on a girl born at 32 weeks of gestation with a birth weight of 1560 g (Table 3). On day 13 she had a plasma Phe level of 1879 μmol/L. She had a Phe tolerance of less than 90 mg/kg/d and needed between 270 and 290 mg/kg/d of Tyr to achieve a normal weight gain. The authors concluded that the intake of Tyr seemed to be a growth limiting factor.[13] Randall *et al*. described a boy born at 30 weeks of gestation with a birth weight of 2360 g and an initial Phe level of 1926 μmol/L on day 19 (Table 3). After cessation of natural protein intake Phe plasma levels normalized rapidly, but upon reintroduction of Phe he needed a Phe intake as high as 100 mg/kg/d to maintain plasma Phe levels in the low normal range. Elevated Phe requirements normalized at term. The authors concluded that preterm infants with classical PKU may require higher phenylalanine intakes in order to meet demands of growth.[12] Hennermann *et al.* described a premature girl (27 weeks of gestation, birth weight 1080 g) known to be heterozygous for classical PKU due to prenatal diagnosis in a context of a positive family history (Table 3). On day 6 while on parenteral nutrition with a Phe intake of 160 mg/kg/d, she had a slightly elevated serum Phe level of 400 μmol/L that further rose to 515 μmol/L on day 8. A Phe-restricted parenteral and enteral nutrition was necessary to maintain normal serum Phe levels until the 42nd day of life. At term serum Phe levels had normalized. The authors hypothesize that heterozygosity for PKU might be a risk factor for transient hyperphenylalaninemia in preterm infants and could be explained by the combination of immature liver function and the genetically determined reduced PAH activity.[11]

Our patient is the most premature reported PKU patient so far, with the longest reported neurodevelopmental follow-up. Despite a long period (17 days) of highly elevated Phe levels in the postnatal period he shows normal psychomotor development without neurological impairment. Given the known toxicity of high Phe blood levels on the developing brain[14-16] and the irreversible brain damage that it can cause in newborns when exposed to it even for short periods of time,[2] the outcome of our patient suggests that the premature brain may still have enough plasticity to overcome the insult of at least 2 weeks of extremely high Phe concentrations. Furthermore, it is possible that brain damage has been limited by prompt availability of sufficient Tyr and other large neutral amino-acids through the parenteral amino-acid solution, and the early supplementation of long-chain polyunsaturated fatty acids (LCP) which are supposed to be involved in neural and cognitive development of preterm infants.[17]

Our patient remained free of the frequent complications of enteral feeding in prematurely born infants. The occurrence of one of these complications would have made management much more difficult.

Table 2. Comparison of composition between the amino acid solutions Aminosteril Hepa 8% and Vaminolact for parenteral use: Vaminolact is the normally used product for parenteral nutrition in preterm infants in our hospital. Aminosteril Hepa 8% is a product designed for patients with liver diseases with low content of phenylalanine and was therefore suitable for application in our PKU patient. It does not contain any tyrosine, but our patient maintained sufficient Tyr plasma levels with the application of little amounts of Phe-free formula.

	Aminosteril® Hepa 8%	Vaminolact®
L-Isoleucine	10.40 g/L	3.1 g/L
L-Leucine	13.09 g/L	7.0 g/L
L-Lysine	6.88 g/L	5.6 g/L
L-Methionine	1.10 g/L	1.3 g/L
L-Cysteine	0.52 g/L	1.0 g/L
L-Phenylalanine	0.88 g/L	2.7 g/L
L-Threonine	4.40 g/L	3.6 g/L
L-Tryptophane	0.70 g/L	1.4 g/L
L-Valine	10.08 g/L	3.6 g/L
L-Arginine	10.72 g/L	4.1 g/L
L-Histidine	2.80 g/L	2.1 g/L
L-Alanine	4.60 g/L	6.3 g/L
L-Glycine	5.82 g/L	2.1 g/L
L-Proline	5.73 g/L	5.6 g/L
L-Serine	2.24 g/L	3.8 g/L
L-Aspartic acid	-	4.1 g/L
L-Glutamic acid	-	7.1 g/L
L-Tyrosine	-	0.5 g/L
Taurine	-	0.3 g/L
Total amino acids	80.00 g/L	65.3 g/L
Total calories	320 kcal/L	240 kcal/L

Table 3. Reported cases of premature infants with PKU.

Reference	Sex	Diagnosis	Gestational age	Birth weight	Age at diagnosis	Max. Phe level
Cole *et al.* 1984[10]	F	PKU	<32 weeks	1480 g	12 days	5670 μmol/L
Shortland *et al.* 1985[13]	F	PKU	32 weeks	1560 g	13 days	1879 μmol/L
Randall *et al.* 2000[12]	M	PKU	30 weeks	2360 g	19 days	1926 μmol/L
Hennermann *et al.* 2004[11]	F	Heterozygous for PKU	27 weeks	1080 g	8 days	515 μmol/L

Conclusions

Even if the concurrence of significant prematurity (in CH 1:100 for <32 weeks of gestation) and PKU (in CH 1:8000) is rare (1:800,000), there is a clear need for appropriate Phe-free parenteral nutrition in order to guarantee optimal treatment in PKU patients with gastro-intestinal complications of prematurity. In the absence of a specific Phe-free parenteral nutrition, amino acid solutions used for hepatic disorders are more appropriate than classical amino acid solutions for prematurity, because of their high content of essential amino acids and relatively low amount of aromatic amino acids. At present, dietary treatment of premature infants with PKU depends on the baby's tolerance of enteral nutrition.

This case points out the importance of a timely diagnosis of PKU in premature babies, as these patients are likely to receive high amounts of parenteral proteins during the first weeks of life. Due to efficient logistics of newborn screening in our country, the turnaround time of results is limited to 2-3 days; therefore diagnosis is usually made within the first week of life. This may not be the case in other countries where preterm PKU babies may be exposed for longer time to extremely high Phe levels.

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