Case Report

Dietary management of maternal phenylketonuria with glycomacropeptide and amino acids supplements: A case report

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ABSTRACT

Background: In maternal PKU, protein substitute (PS) is provided by phenylalanine (PHE)-free L-amino acids (AA), but glycomacropeptide-based protein substitute (GMP) is an alternative consideration.

Objective: To describe the first Portuguese Maternal Phenylketonuria (MPKU) partially managed with GMP.

Case report: A 31 year old MPKU female with classical PKU (mutations P281L/P281L), diagnosed by newborn screening, had a lifelong history of poor metabolic control. She has a history of partial bicornuate uterus and had a previous miscarriage in the first trimester. Pre-conception, her median blood PHE was 462 μmol/L but throughout pregnancy the median reduced to 258 μmol/L. GMP provided 30 g/day protein equivalent (46 mg/day PHE). Total protein equivalent from PS increased from 58 to 86 g/day during pregnancy but AA provided all additional protein equivalent intake. Both GMP and AA were well tolerated with no morning sickness. Normal morphologic evaluation and adequate fetal growth with cephalic biometry near the 5th percentile was determined. The infant was born at 39.3 weeks: weight 2570 g (3rd percentile), length 47.5 cm (10th percentile) and head circumference (HC) of 31.5 cm (1st percentile). In the neonatal period, the infant had craniofacial dimorphism with metopic suture prominence. Father also had bitemporal narrowing. By 12 months of age, the infant's weight (15th percentile), length (50th percentile) and HC (10th–50th percentile) were normal although bitemporal narrowing persisted.

Conclusions: This is the first case reporting the use of GMP in MPKU. Its PHE content did not adversely affect metabolic control although it only provided part of the PS intake. Some intrauterine development delay occurred in the last trimester, although we consider that this is unlikely to be associated with MPKU syndrome or the use of GMP. More published data is essential to examine the impact of using GMP in MPKU on morning sickness severity and aversion, maternal weight gain, blood amino acid concentrations and variability of blood PHE concentrations.

1. Introduction

Maternal phenylketonuria PKU (MPKU) syndrome [1–3] was first described over 60 years ago [4]. There is a convincing correlation between high maternal blood phenylalanine (PHE) concentrations, particularly during critical periods of embryogenesis in early pregnancy and fetal abnormalities including fetal growth retardation, microcephaly, and structural heart defects [1–3]. There is also a relationship between poor maternal nutritional status and infant microcephaly,

decreased fetal growth and congenital heart defects [5,6]. Therefore, in MPKU it is crucial to achieve satisfactory maternal nutritional status together with optimal blood PHE control pre-conception and sustain this throughout pregnancy [7,8].

MPKU is managed by a strict low PHE diet (commonly ≤ 6 g/day natural protein is tolerated in the early stages of pregnancy but PHE amount is dependent on PKU severity), together with a PHE-free L-amino acid supplement (AA) (supplemented with tyrosine, vitamins, minerals and commonly EPA/DHA), and sufficient energy intake to

ensure adequate maternal weight gain during pregnancy [9,10]. The protein equivalent from AA and natural protein should supply ≥ 70 g/day protein equivalent [8]. Additional tyrosine supplements may be necessary if intake is < 6 g/day from AA [8]. Dietary management is challenging [11] because some women may have relaxed or stopped their low PHE diet therapy prior to pregnancy and therefore find it particularly demanding to adhere to the prescribed amounts of AA [6,12,13]. Nausea and vomiting during the early phases of pregnancy is common and may lead to inadequate intake of AA and energy [10,14] and unsatisfactory blood PHE control [14].

In 2003, it was described that glycomacropeptide could be extracted from sweet whey [15]. Unmodified glycomacropeptide is without the amino acids histidine, tyrosine, tryptophan, cysteine, arginine, and contains low amounts of leucine and methionine. The large neutral amino acids, threonine and isoleucine, are two to three times higher than the amounts added to conventional AA. Commercial glycomacropeptide based protein substitutes (GMP) are now available for PKU. They are supplemented with leucine, histidine, methionine, tryptophan and tyrosine but also contain some residual PHE (PHE = 1.8 mg/g of protein equivalent) due to contamination during the glycomacropeptide extraction process. Thereby, 20 g protein equivalent provided by a GMP supplement will provide an additional 36 mg/day PHE. GMP is associated with improved patient taste, adherence and smell [16] and may be beneficial for MPKU when women are unable to accept or tolerate traditional AA, particularly with hyperemesis.

There is no peer reviewed evidence reporting the use of GMP in the management of MPKU. It is unknown if it is safe or well tolerated and the impact of its PHE content is not described in MPKU. The objective of this paper is to present a female PKU patient from Centro Hospitalar do Porto, Portugal, taking GMP as part of her protein requirements during pregnancy. Written informed patient consent was given prior to the publication of this case report.

2. Case report

A 31 year old MPKU female was diagnosed by newborn screening, with a neonatal blood [PHE] level of 1260 μmol/L, categorized as classical PKU when blood [PHE] > 1200 μmol/L according to the Portuguese Nutritional Consensus [17]. Genotype analysis indicated the P281L mutation in both alleles.

A low PHE diet was commenced at 18 days of age. Unfortunately, since 1 y of age, she was unable to fully adhere with dietary restrictions and almost all her blood [PHE] levels were above the Portuguese Nutritional Consensus [17] upper target range (aged < 12 y: 120 to 360 μmol/L and aged > 12 y; 120 to 480 μmol/L (Fig. 1). During her first year of life, the annual median blood PHE was 300 μmol/L but by the age of 2 y, this had increased to a median blood PHE of 720 μmol/L. Since the age of 3 y, median values were consistently > 1200 μmol/L until pre-conception and pregnancy (Fig. 1).

At the age of 8 y, her IQ was 77 assessed with "The Stanford–Binet Intelligence Scales" [18]. When repeated at age 28 y, using the Wechsler Adult Intelligence Scale (WAIS-III) [19], her global IQ was 68. She had learning difficulties at school, received a special education program and did not progress beyond elementary school level. Psychological assessments consistently identified high anxiety levels and low self-control. She received little maternal support throughout life. She attempted several jobs but failed to maintain any of them. She had a history of partial bicornuate uterus and miscarriage.

At 24 y, she commenced pre-conception dietary treatment with the aim of maintaining blood PHE within the Portuguese Nutritional Consensus [17] target range of 120–360 μmol/L but preferably 120–240 μmol/L, for at least 2 weeks prior to conception. Blood PHE levels were measured with fasting blood spots twice weekly during pre-conception and pregnancy.

A diet restricting natural protein (PHE intake 658 mg/day), and supplemented with special low protein foods and a combination of GMP

(Bettermilk®) and AA (PKU3 Advanta®) was implemented. Folic acid, and general vitamin and mineral supplementation was given before and during pregnancy. Throughout dietary treatment, she was supported by her partner and mother in law who helped with meal preparation and overall dietary management.

The case study had a sapropterin® loading test two months prior to pregnancy, with a blood PHE reduction of 35%. The multidisciplinary team chose not to treat her with BH4 during pregnancy when she had not received prior treatment with this drug.

She only consistently achieved blood PHE within target range when she reported her pregnancy at 4 weeks' gestational age. Metabolic control during pregnancy is presented in Fig. 2. Median blood PHE during pregnancy was 258 μmol/L (Fig. 2) compared with 486 μmol/L pre-conception diet (Fig. 1).

Nutritional intake during pregnancy is described in Table 1. GMP was started 18 months prior to pregnancy. She took 30 g/day of protein equivalent from Bettermilk® (2 × 15 protein equivalent sachets/day providing 45 mg of PHE/day), with the remaining protein substitute (PS) supplied by AA (PKU3 Advanta®), providing 28 g/day of protein equivalent. She remained on the same amounts of GMP throughout pregnancy. The AA was increased to 42 g/day of protein equivalent at 16 weeks and to 56 g at 18 weeks' gestation (Table 1). The percentage of protein equivalent provided by GMP decreased throughout pregnancy (52% at 4 weeks, 42% at 16 weeks and 35% at 18 weeks, respectively).

At pregnancy notification (gestational age 5 weeks), PHE intake from natural protein sources was reduced to 458 mg/day to improve metabolic control (Table 1). By 7 weeks of pregnancy, PHE tolerance had increased to 643 mg/day (Table 1). PHE intake was not reduced to compensate for the PHE content of GMP (Fig. 2 for blood PHE control during preconception and throughout pregnancy). Median blood tyrosine levels measured by fasting blood spots were 43 μmol/L (n = 29 samples) until 16 weeks of pregnancy and 51 μmol/L (n = 46 samples) after 16 weeks.

The case study did not report any nausea or vomiting during pregnancy, which assisted good adherence with both GMP and AA supplements. Adherence was better with both PS compared to her pre-pregnancy history. Increasing intake of AA supplements was well tolerated.

Biochemical analyses are reported prior, during and post-pregnancy (Table 2). An oral glucose tolerance test at 21 weeks was not abnormal (blood glucose of 84, 94 and 86 mg/dL at 0, 60 and 120 min respectively, with ingestion of 75 g of glucose). Selenium and zinc concentrations were below normal ranges during pregnancy (0.44 and 7.48 mmol/L, respectively).

Maternal weight gain during pregnancy was 15 kg (for a pre-pregnancy BMI of 23, recommended weight gain is between 11.5 and 16 kg [20]).

2.1. Intrauterine development and anthropometric development

A combined risk assessment positive for trisomy 18 and 13 was detected by low *βeta-unit human chorionic gonadotropin* (BhCG) and *pregnancy-associated plasma protein-A* (PAPP-A) at 10 weeks. Maternal weight gain (15 kg) was normal during pregnancy. There was normal morphologic evaluation and adequate fetal growth with cephalic biometry (an indicator of fetal head shape) near the 5th percentile.

2.2. Delivery

An elective cesarean delivery, for breech presentation was scheduled at 39.3 weeks gestational age. The infant birth weight was 2570 g (3rd percentile), with a length of 47.5 cm (10th percentile) and head circumference of 31.5 cm (1st percentile). In the neonatal period, the infant had craniofacial dimorphism with metopic suture prominence.
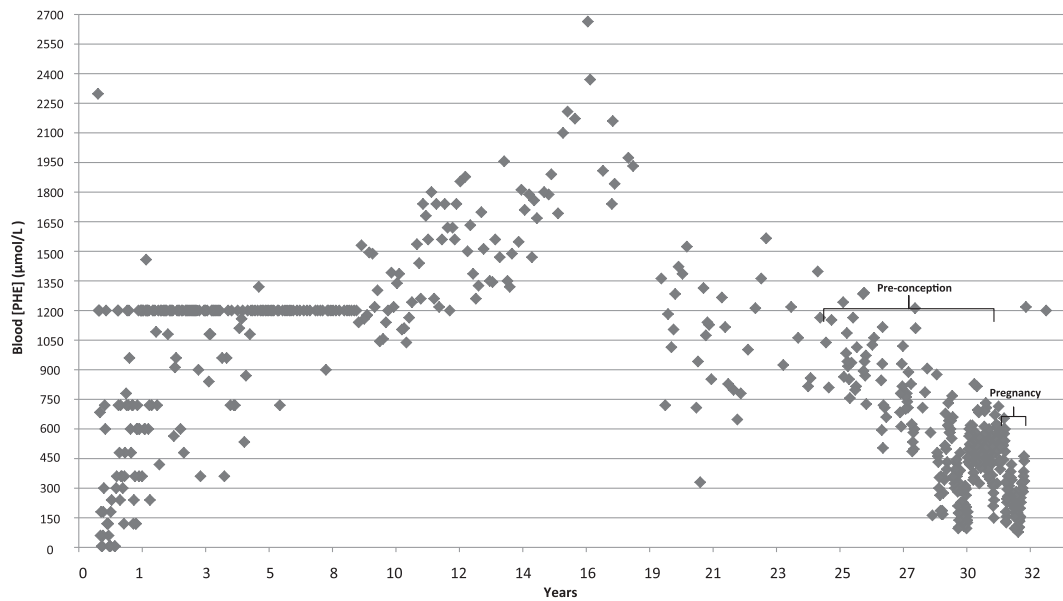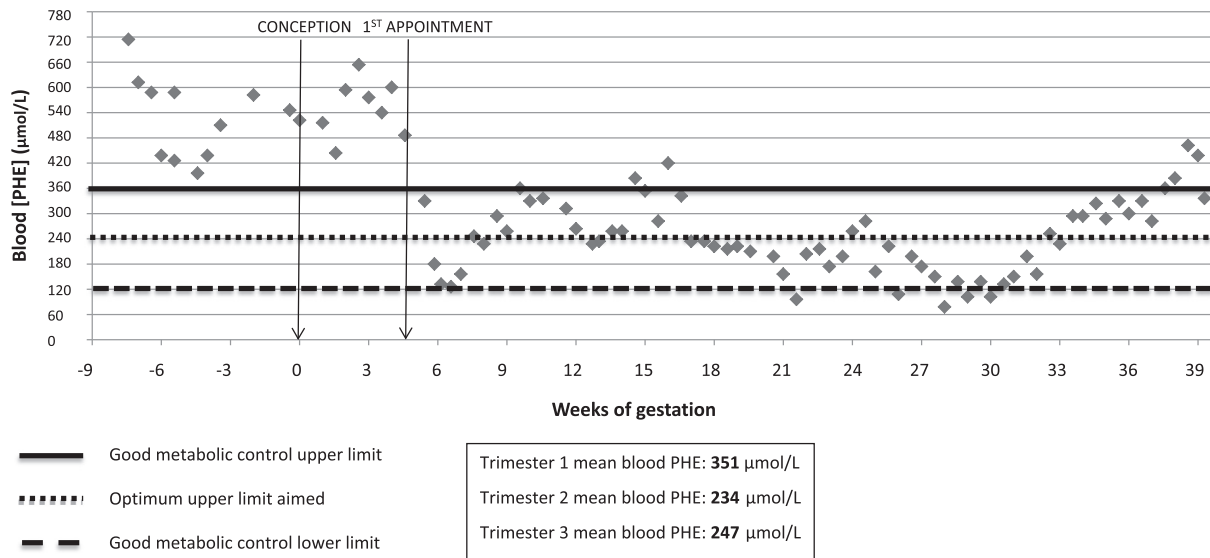
Fig. 1. Blood PHE concentrations (μmol/L) throughout life.

Trimester 1 mean blood PHE: **351** μmol/L		
Trimester 2 mean blood PHE: **234** μmol/L		
Trimester 3 mean blood PHE: **247** μmol/L		

Fig. 2. Blood PHE concentrations (μmol/L) during pregnancy.

2.3. Infant progress post delivery

At 12 months of age, the infant's weight (15th percentile) and length (50th percentile) were considered adequate. At 15 months, the Griffiths Mental Development Scales for Children indicated that he had a global development age of 13.6 months and a normal Global DQ of 91 (normal DQ values ≥ 85), but his locomotor skills were delayed and he was unable to crawl. His head circumference was on the 15–50th percentile. Bitemporal narrowing persisted. The father also had bitemporal narrowing.

2.4. Maternal management post-pregnancy

Post-partum, the case study returned to an unrestricted diet, without any PS. After 8 months, post-delivery, body composition analysis showed she had not been able to lose the weight and fat mass gained during pregnancy. She did not breast feed.

3. Discussion

This is the first peer reviewed case study to report the use of GMP in the dietary management of MPKU. PHE GMP content was well tolerated during pregnancy, although GMP only contributed 52% of the total PS intake, decreasing to 42% at 16 weeks and finally to 35% at 19 weeks. The case study had good metabolic control with almost all blood PHE levels below 252 μmol/L except during the first 5 weeks of pregnancy but she still maintained a median Phe level of 258 μmol/L during pregnancy.

A review of abstracts on case studies of women with MPKU [21] taking GMP reported 2 women with 3 pregnancies taking both GMP and AA, but GMP only contributed on average 15% of total PS intake. Mean blood PHE levels were within target ranges (181 μmol/L) and infant outcome was normal (mean HC and weight z-scores were − 0.76 and − 0.47, respectively). A further 4 patients with 4 infants, also pre-scribed sapropterin®, took all their PS requirements from GMP. Overall, good outcome was achieved with a mean PHE level of 157 μmol/L and HC and weight z-score of − 0.48 and − 0.08 respectively. However, one

Table 1
Nutritional intake and body weight pre, during and post-pregnancy.

	Pre-pregnancy 1	Pre-pregnancy 2	Pre-pregnancy 3	5 weeks	6 weeks	7 weeks	12 weeks	16 weeks	19 weeks	24 weeks	27 weeks	30 weeks	34 weeks	36 weeks	38 weeks	Post-partum
Natural protein (g/day)	15	15	15	9	12	12	12	16	16	16	21	29	30	30	29	89
Total protein equivalent intake from protein substitute (g/day)	58	58	58	58	58	58	58	72	86	86	86	86	86	86	86	0
GMP (g of protein equivalent/day)	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	0
AA (g of protein equivalent/day)	28	28	28	28	28	28	28	42	56	56	56	56	56	56	56	0
Total tyrosine from protein substitute (g/day)	4.9	4.9	4.9	4.9	4.9	4.9	4.9	6.1	7.2	7.2	7.2	7.2	7.2	7.2	7.2	0
Tyrosine from GMP (g/day)	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	0
Tyrosine from AA (g/day)	2.2	2.2	2.2	2.2	2.2	2.2	2.2	3.4	4.5	4.5	4.5	4.5	4.5	4.5	4.5	0
Phe (mg/day)	651	665	658	458	628	643	643	853	793	808	1024	1439	1425	1420	1420	4271
Total energy intake (kcal/day)	2821	2779	2683	2490	2681	3026	3026	3419	2929	3525	3888	3735	3496	3450	3450	2259
SLPF (kcal/day)	1300	1258	1162	1211	1355	1700	1700	1889	1340	1936	1956	1533	1294	1248	1248	0
Body weight (kg)	61.0	62.5	62.0	64.0	64.5	66.0	66.0	68.0	69.0	71.0	71.5	73.5	74.5	76.0	77.0	70.0

GMP: glycomacropeptide-based protein substitute.
PHE: phenylalanine.
SLPF: special low protein foods.
Pre-pregnancy 1, 2 and 3 regard the 3 previous appointments to pregnancy.

Table 2
Biochemical analysis pre, during and post-pregnancy.

Biochemical markers	Pre-pregnancy	During pregnancy	Post-pregnancy (non-compliant)
Uric acid (mg/dL)	2.8	–	3.3
Glucose (mg/dL)	75	79	92
Creatinine (mg/dL)	0.61	–	0.64
Urea (mg/dL)	19	19	25
Haemoglobin A1C (%)	4.4	4.3	4.5
Total cholesterol (mg/dL)	127	**226**	165
Triglycerides (mg/dL)	38	**164**	43
HDL cholesterol (mg/dL)	52	**95**	50
LDL cholesterol (mg/dL)	67	98	106
VLDL cholesterol (mg/dL)	8	**33**	9
Apolipoprotein A1(mg/dL)	138	**269**	129
Apolipoprotein B (mg/dL)	74	109	76
Iron (µg/dL)	123	95	97
Transferrin (mg/dL)	238	**380**	248
Ferritin (ng/mL)	36	–	40
Albumin (g/dL)	4.43	**3.42**	4.33
Homocysteine (µmol/L)	7.3	5.41	9.56
Prealbumin (mg/dL)	**190**	218	239
C-reactive protein (mg/dL)	0.82	**6.13**	3.79
Insulin (µU/mL)	7.5	6.7	9.5
Calcium (mmol/L)	2.19	2.16	2.30
Phosphorus (mmol/L)	**0.79**	0.94	0.90
Plasma selenium (mmol/L)	0.63	**0.44**	1.03
Plasma zinc (µmol/L)	12.4	**7.48**	**7.54**
Vitamin.B$_{12}$ (pg/mL)	459.2	294.5	390.9
Vitamin D (nmol/L)	52	78	57
Folic acid (ng/mL)	> 20	**19.9**	7.5
Haemoglobin (g/dL)	13.5	13.2	13.3

Bold values signifies measurements out of the reference range.
HDL: high density lipoprotein.
LDL: low density lipoprotein.
VLDL: very low density lipoprotein.

infant had a low birth weight but treatment started during pregnancy and sapropterin® was stopped for 10 days in the first trimester.

Although GMP is not free of PHE, it only provided 45 mg/daily PHE and our case quickly achieved blood PHE target ranges on pregnancy notification. PHE in GMP is considered disadvantageous but it may have potential benefits later in pregnancy. PHE tolerance significantly increases in the second trimester onwards, associated with fetal-maternal anabolism and some women find it difficult to eat their daily PHE allowance in the latter stages of pregnancy. Our MPKU doubled her natural protein tolerance by week 34 gestation compared with pre-conception (30 g vs. 15 g, respectively). In addition to the teratogenic effects of PHE, its deficiency is associated with a higher risk of intra uterine growth retardation, particularly if blood PHE is below 120 µmol/L for any length of time in pregnancy [22]. In fact, it is recommended if blood PHE levels decrease below 120 µmol/L in pregnancy, dietary PHE supplementation (50–100 mg/day) should be given [8].

The amino acid composition of GMP is different from AA and its suitability for pregnancy requires careful consideration. In pregnancy, although the ideal large neutral amino-acid/total amino-acid ratio is undetermined, the AA supplements prescribed in pregnancy generally have a lower large neutral amino-acid/total amino-acid ratio [23]. In contrast, the percentage of large neutral amino acids in GMP are higher than AA [23]. We chose to meet increasing protein requirements in pregnancy with AA rather than GMP due to inexperience of using GMP

in MPKU and lack of supporting quantitative amino acid and outcome data. Our patient had a tyrosine intake (4.9 g/day) which was below the European guidelines at the start of pregnancy but later met recommendations when AA was increased in pregnancy (6.0 and 7.2 g/day of tyrosine at 16 and 19 weeks, respectively). Median blood tyrosine concentrations increased from 43 μmol/L ($n = 29$ samples) to 51 μmol/L ($n = 46$ samples), before and after 16 weeks of pregnancy, respectively.

The vitamin and mineral intake from the combination of GMP and AA met recommendations throughout pregnancy. Our case had decreased plasma selenium and zinc concentrations during pregnancy. A low zinc concentration may be associated with an excess of folic acid intake which may interfere with zinc homeostasis [24] but is likely to be associated with the maternal, placental and fetal adaptations taking place in pregnancy [25]. Other biochemical abnormalities may be due to physiological consequences of pregnancy rather than clearly mirroring nutritional status (triglycerides, total cholesterol, HDL cholesterol, VLDL cholesterol and c-reactive protein). Protein status is also difficult to analyse as this case study had lower albumin but a higher pre-albumin concentration. A limitation of our data is that quantitative plasma amino acids were not measured. It is recommended that supplementation with 200 mg of docosahexaenoic acid (DHA) is given in pregnancy for fetal growth [8]. GMP contained DHA and arachidonic acid but only provided 77 mg/day of DHA and 1 mg/day of arachidonic acid in 30 g of protein equivalent.

Intrauterine growth was within normal reference range, but decreased to near the 5th percentile in the last trimester. Adequate nutrition during the last trimester is important for fetal growth and this is influenced by nutritional deficiencies in addition to blood PHE control [5,6]. At delivery, the newborn infant presented with craniofacial dimorphism with metopic suture prominence and although he had a normal Global DQ at 15 months, locomotor skills were delayed. We consider it unlikely that GMP contributed to this infant abnormality as the patient had good metabolic control from week 5 of pregnancy, immediately post pregnancy notification. Also the case study had a partial bicornuate uterus and father had bitemporal narrowing. By 15 months' post gestation, the infant had achieved a HC on the 10–50th percentile.

The weight gain of this MPKU case was within the normal expected range [20]. The GMP prescribed had a higher energy content compared with AA, and this may have helped to meet energy requirements in pregnancy and avoid catabolism. Although her life-time adherence to diet and PS was poor, like many other MPKU cases [26,27], she was very motivated in pregnancy and managed to consume the prescribed amounts of the two PS without any morning sickness. It is unknown if GMP contributed to the absence of morning sickness, although it is associated with improved palatability [28–30].

This is the first case study to report the use of GMP in the management of MPKU. Although some intrauterine development delay occurred in the last trimester of pregnancy, it is considered this was unrelated to either the use of GMP or MPKU syndrome. More data is essential to examine the impact of using GMP in MPKU particularly with respect to morning sickness severity, maternal weight gain, blood amino acid concentrations and variability of blood PHE concentrations.

Conflicts of interest

Acknowledgment

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