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Growth and Nutritional Status of Children with Urea Cycle Defects (UCD): A 6-months Follow up Study in Institute of Pediatric, Hospital Kuala Lumpur

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Abstract Poor growth has always interlinked with urea cycle defects children who require life-long protein restricted diet. Studies have proposed the prolonged restriction on essential amino acid could cause the damage especially malnutrition, which make the patient susceptible to infections and immune deficiencies, events that can become even more dangerous than the original disease. By far there is no study reported in the context of nutritional status among children with Urea Cycle Defects (UCD), who receiving active regular medical and dietary treatment. Hence, the aim of this single-center 6-months follow-up study was to determine nutritional status of children diagnosed with UCD. A total of 22 children with UCD, aged from 1 to 12 years old (mean: 6.04±2.40) undergoing active regular treatment in Institute of Pediatrics were recruited. Body height, weight, and head circumference were measured for anthropometry whereas total protein, albumin and plasma amino acid profile were investigated for biochemical aspects. Clinical features diagnosed by pediatrician were recorded from children's medical record. 24 hour dietary recall was conducted to measure their nutrients intake. All assessments were repeated at 6-month interval except clinical profile. Overall, there were no significant differences $p>0.05$ in means of z-scores of all nutritional parameters from baseline to end of the visit. There was suggestive of a prominence in growth stunting (67; 61%), undernutrition (44; 30%) and microcephalic (33; 33%) among children with UCD. Biochemical indicators such as citrulline, albumin and total protein (only during follow up) were significantly ($p<0.05$) higher than the reference value, however, in this case, only citrulline (529±888; 573±883 μmol/L) require more attention from physician. Intellectual disability was the most frequently (71%) presenting sign and symptoms among UCD children. The present finding also did not found intake of any macro and micronutrients that fall short of recommended intake judging from the figures reported from combination of both resources (>100% RNI) in both visits except intake of vitamin A, B3, and C from natural food were significant lower ($p<0.05$) during follow up. In conclusion, all these findings indicated that UCD children are definitely at risk of malnutrition and regular nutritional assessment and monitoring should always emphasised for optimal linear growth without affecting their amino acid profiles.

Keywords: *Inborn Errors Metabolism, Urea Cycle Defects, nutritional status, Hospital Kuala Lumpur*

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1. Introduction

The urea cycle is the metabolic pathway that eliminates excess nitrogen of the body by detoxification of ammonia into urea (Gonzalez et al, 2010). Inherited urea cycle disorders comprise six disorders (UCD), each caused by a deficiency in one of the urea cycle enzymes, carbamoylphosphatesynthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinatesynthetase (ASS), argininosuccinatelyase (ASL), 1- arginase (ARG1) and N-acetylglutamate synthase (NAGS) that is essential for ureagenesis (Brendan, 2012).

Partial or total absence of any of these enzymes will not only lead to respective protein deficiencies (abbreviated CPS1D, OTCD, ASSD, ASLD, ARG1D and NAGSD; corresponding MIM numbers, #237300, #311250; #215700; #207900; #207800; #237310 respectively) (Häberle et al, 2012) but also predispose patients to episodiclife-threatening hyperammonemia (Gregory, 2008). Elevation of blood ammonia will result in accumulation of glutamine, leading to cerebral edema, and

encephalopathy (Felipo, 2002), which involves awide spectrum of neuropsychiatric and neurological symptoms such as impaired memory, shortened attention span, sleep–wake inversions, seizures, and coma (Bosoi, 2009).Studies also reported that this condition is constantly associated with a high degree of mortality (~50%) (Häberle et al, 2012) and morbidity (Tuchman, 2008), however, the character manifestation and severity of hyperammonemia is still depending on the affected enzyme and its residual activity (Summar, 2008).

Generally, UCDs are inherited in autosomal-recessive traits, except for the deficiency of OTC, which is X-linked (Häberle, 2013). According to Haberle et al (2012), the worldwide prevalence UCD may exceed the current estimates 1:8,000-1:44,000 births, because of unreliable newborn screening and underdiagnosis of fatal cases. In the United States, UCD prevalence is estimated to be between 1 in 8,200 and 1 in 25,000 live births (Summar, 2008) and in Japan, UCDs represent one of the most common groups of inborn errors of metabolism, with an estimated prevalence of 1 in 50,000 (Uchino et al, 1998). Nevertheless, in Malaysia, the actual UCD prevalence figure from 2008-2013 is remained unknown due to lack of local longitudinal studies; however, a local study conducted by Thong et al (2008) indicated a prevalent of 0.40% (54 diagnosed as UCD) from 13400 Inborn Errors Metabolism cases in Malaysia.

The Institute of Pediatrics of Hospital Kuala Lumpur located in Selangor, Malaysia, is one of the pioneer institutes in setting up the service for Inborn Errors of Metabolism children since 1985. It is the only institution in Malaysia which has catered with additional financial aid, approximately RM1, 700,000.00 to 1, 800, 000.00 annually from Ministry of Health (MOH) to provide free medical care and most importantly, medical food supplies in order to sustain the life of IEMs children (HKL, 2010). Besides, the pathology laboratory unit from the hospital also receives samples for investigations of Inborn Metabolic Diseases in all regions of Malaysia. Up until end-2013, 38 UCD children has been diagnosed and undergoing active regular treatment in the metabolic clinic of HKL (HKL, 2013).

Dietary treatment is a cornerstone of UCD therapy. It consists of a protein-restricted diet supplemented with an EAA mixture high in branched-chain amino acids (BCAAs) (Brendan, 2012). The aim is to prevent elevation of both endogenous and exogenous waste nitrogen and ensure adequate intakes of essential and conditionally essential amino acids (Adam et al, 2013). In addition, administration of sufficient protein-free energy is crucial to permit the normal turnover of protein necessary at all ages and to minimise catabolism of body stored protein (Singh, 2007).

Morton et al. (2006) reported that any condition which requires prolonged restriction on essential amino acid could easily cause the damage like malnutrition, which make the patient susceptible to infections and immunodeficiencies, events that can become even more dangerous than the original disease. In other words, UCD children are definitely at a higher risk for poor growth, motor disorders and neurocognitive disorders as they require lifelong dietary protein restriction (Acosta, 2005). Apart from the study conducted by Acosta et al (2005) which indicated significant length and weight z-scores improvement of seventeen UCD children during 6-month of nutrition therapy, up to the current established knowledge of this subject, no found of any other comprehensive studies published regarding nutritional status profile of UCD children across the worldwide or to explore the duration required in order to observe a significant improvement on nutritional status profile of IEMs children who already receiving the medical and dietary food intervention in their early life. With this, this study empirically assesses nutritional status of children with UCD who receiving regular active medical and diet treatment at 6-month interval.

Finding from this study not only allows yielding important first time insights into the natural history but also prospective aspect of their anthropometric, biochemical, clinical and dietary that characterise UCD. Besides, these data are likely to markedly improve our understanding of these devastating disorders and offer better approaches to their treatment. Furthermore, it aims to enhance the awareness on the role of earlier diagnostic and screening of UCD disorders among the high risk group and family. Nevertheless, the main benefits from this effort will only be occurred after years of prospective study of enrolled patients, with full participation of many clinical centres.

2. Methods

2.1. Research Design

This is a single-center 6-months follow-up of nutritional status in children with MSUD. This research successfully registered at National Medical Research Register (NMRR)-13-495-16038 and approved by Institute of Health Behavioural Research (IHBR), Hospital Kuala Lumpur (HKL/TAD/98/180/5) as well as Research Ethnics Committee from UniversitiKebangsaan Malaysia. This observation study used two linked datasets for the analysis on the same subjects at 6 month interval (Figure 1): a preliminary baseline dataset collected from March 2013 to June 2013 and data for the follow-up study from September 2013 to December 2013.

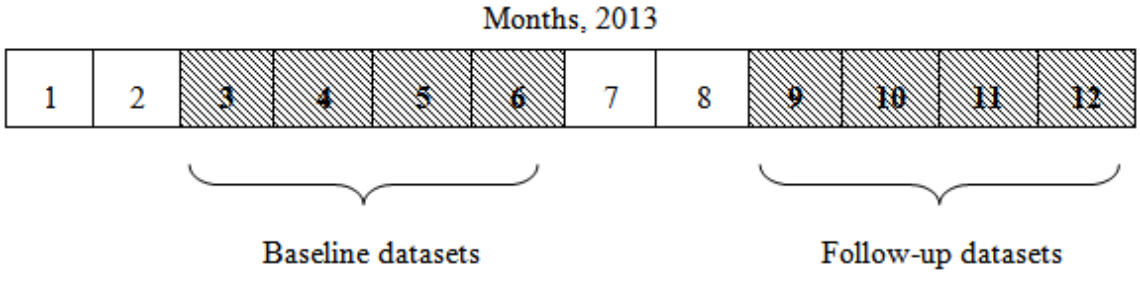

Figure 1. Six-month follow-up on UCD children

2.2. Subjects

This study was conducted on 18(7 male, 11 female) children with UCD, aged between 1-12 years at metabolic clinic of institute pediatric, Hospital Kuala Lumpur between January 2013 and December 2013.Universal sampling method was applied in the study. The aim and content of the study has been explained to families of children. Caretaker of children signed a voluntary participation form which approved by Hospital Kuala Lumpur (HKL/TAD/98/180/5) and Research Ethnics Committee from UniversitiKebangsaan Malaysia. A questionnaire about child and family's descriptive information was conducted by face to face interview with caretaker of children.

2.3. Anthropometric Assessments

For evaluation of children's growth, anthropometric measurements (Lee & Niemen, 2007) were performed by researchers. Measurement of body weight (SECA 803) was performed with light clothes and with a scale nearest to 0.1 kg. Height was measured while foots are collateral and head was in Frankfort plane. In children who aged less than 2 years the height measurements were performed with infantometer (SECA 210) in laying position. Head circumferences were measured the distance from above the eyebrows and ears (occipital – frontal process) and around the back of the head with a scale nearest to 0.1 cm. The anthropometric indicators used to evaluate data were z-score of weight-for-age, height-for-age and head circumference-for-age. Mean z-scores of these parameters were computed with the software of WHO standards (2006) and WHO reference (2007) in its website:http://www.who.int/childgrowth/software/en/ and http://www.who.int/growthref/tools/en/ respectively.

2.4. Biochemical Measurements

Children's plasma amino acid (ammonia, alanine, arginine, citrulline, and glutamine), level were analysed with amino acid analyzer (Biochrom 30) by ion exchange chromatography method (Yunus, 2011) while total protein and albumin level were analysed by the method of colorimetric assay and bromocresol green respectively. All measurement and analysis were conducted by biochemistry staff of pathology laboratory unit in Institute Pediatrics, Hospital Kuala Lumpur.

2.5. Clinical Assessments

Presenting signs and symptoms of UCD children were reviewed retrospectively from their medical records which were diagnosed by pediatrician.

2.6. Dietary Assessments

24-hour dietary recall was conducted via face to face interview with the caretaker of UCD children. Analysis of dietary intake was done using the computerised Nutritionist Pro software version 4.0.0 (Axxya System, U.S.), which calculated nutrients intake according to Malaysian Food Composition Table (Tee et al. 1977). Singapore Food Composition was used to supplement the micronutrients(Zinc and Selenium) databases. Dietary adequacy was assessed by comparison of energy and nutrient intake with the Recommended Nutrient Intakes(RNIs) for Malaysians (NCFFN, 2005). Adequacy macro and micronutrients was considered achieved if the children's mean percentage intake met or exceed, at a minimum of 100% of the RNI. Each nutrient was presented as follows, combination of natural and medical food, solely natural or medical food in order to provide a better picture of the percentage contribution from each resource in daily intake of UCD children.

2.7. Statistical Analyses

Data were evaluated with SPSS 21.0 Statistical Package Program. Number and percent of descriptive data were calculated. Mean and standard deviation values were presented in tables and graph. Statistical significance was established at a p value of less than 0.05.

3. Result

3.1. Characteristic and Socio-demographic Profile

Table 1. Characteristic and demographic information of UCD Children

Variables	Mean (SD)	Frequency (%)
Present Age (years)	6.04 (2.40)	18 (100)
Birth Weight (kilogram)	3.15 (0.43)	18 (100)
Breastfeeding (days)	20.11(52.02)	18 (100)
Ethnicity		
Malay		17 (94.40)
Chinese		1 (6.60)
Types		
Argininosuccinase acid lyaseDefiency (ASA/ASL)		4 (22.20)
Argininosuccinic acid synthetase Deficiency (CTI/ASD)		4 (22.20)
Ornithine Transcarbamylase Deficiency (OTC)		3 (16.70)
Carbamoyl Phosphate Synthase Deficiency (CPS)		3 (16.70)
Arginase Deficiency (AD/ARGD)		4 (22.20)
State		
Selangor		2 (11.10)
Kuala Lumpur		2 (11.10)
Penang		1 (5.60)
Pahang		3 (16.70)
Kelantan		4 (22.20)
Johor		3 (16.70)
Terengganu		3 (16.70)
Parental Consanguinity		
Yes		6 (33.30)
No		12 (66.70)
Family History		
Yes		1 (6.60)
No		17 (94.40)
Fasting During Ramadhan		
No		18 (100.00)
Number of Sibling with IEMs		
0		13 (72.20)
1-2		5 (27.80)
Monthly Income (RM)	2522.22 (1850.45)	18 (100)
<2300		9 (50)
<2300-5599		5 (27.80)
<5560		4 (22.20)

Table 1 summarises the results with regard to characteristic of all the recruited young Urea Cycle

Defects (UCD) children (n=18), aged between 1–12 years old and the mean of age was 6.04 ± 2.40 years old. There were 7 male (38.9%) and 11 female (61.1%) children. Majority of the children were Malay (94.4%) and the remaining 6.6% were Chinese. Most of them stayed in Kelantan (22.2%), followed by Pahang (16.7%), Johor (16.7%), Terengganu (16.7%), Selangor (11.1%), Kuala Lumpur (11.1%) and lastly, Penang (5.6%) which has the least in number of MSUD children. The mean birth weight and breastfeeding were approximately 3.15 ± 0.43kg and 20.11 ± 52.02 days respectively. Parental consanguinity was found 33.3% of cases and only one (6.6%) out of eighteen cases was related to family history. Next, 27.8% of them had at least 1-2 siblings diagnosed with similar Inborn Errors Metabolic (IEM) disorder, however, majority (72.2%) of them found with no siblings diagnosed with similar IEMs.

3.2. Anthropometry Measures

Table 2 demonstrated comparison mean z-score of those parameters (height, weight, and head circumference) by WHO 2006 and WHO 2007 between baseline and follow-up. Generally, there were slight improvement on mean z-scores of all the parameters (height, weight, and head circumference) between baseline (-2.71±1.58; -1.67±1.73, -2.41±1.82) and follow-up visit (-2.38±1.18, -1.39±1.89, -2.35±1.78), however, no found of any significant differences (p>0.05) in means z-scores of these anthropometric parameters. The results showed that of the 18 subjects between baseline and at the end of the study, 12 (66.6%), 11 (61.0%) were stunted for height-for-age, 8(44.4%), 5 (29.5) were underweight for weight-for-age, and 2 (33.3%), 2 (33.3%) were classified as microcephalic (≤-2SD) forehead circumference-for-age.

Table 2. Mean and standard deviation (SD) of HAZ, WAZ, BAZ and HCZ of 1-12 years UCD children

Anthropometry indicator	Baseline			Follow-up			p-value
	n	Mean (± SD)	%	n	Mean (± SD)	%	
Height-for-age (cm)	18	– 2.71 (1.58)		18	– 2.38 (1.18)		0.058
≤ -3SD (Severely stunted)	8		44.4	7		38.8	0.250
-3 – ≤ -2SD (Stunted)	4		22.2	4		22.2	0.727
> -2SD (Normal)	6		33.3	7		38.8	
Weight-for-age (kg)	18	– 1.67 (1.73)		17	– 1.39 (1.89)		0.566
≤ -3SD (Severely underweight)	7		38.8	4		23.6	1.000
-3 – ≤ -2SD (Underweight)	1		5.6	1		5.9	1.000
-2 – ≤ 0SD (Normal)	7		38.8	8		47.1	1.000
>0SD (At risk of overweight)	3		16.7	4		23.5	1.000
Head Circumference-for-age(cm)	6	– 2.41 (1.82)		6	– 2.35 (1.78)		0.824
≤ -2SD (Microcephalic)	2		33.3	2		33.3	1.000
-2 – ≤ 2SD (Normal)	4		66.7	4		66.7	1.000

Category data tested by Mc Nemar test.

Table 3. Distribution of UCD children's total protein, albumin, plasma amino acid between baseline and follow-up (n=18)

Biochemical indicator (Standard / Unit)	Baseline			Follow-up			p-value
	%	Mean (± SD)	Sig.	%	Mean (± SD)	Sig.	
Total Protein		70.67 (5.08)	0.001		66.01 (6.73)	0.994	0.010
(≥ 66g/L)	83			56			
(< 66g/L)	17			44			
Albumin		42.5 (4.29)	0.000		39.71 (4.94)	0.000	0.040
(≥ 30g/L)	100			100			
Ammonia		58.74 (22.52)	0.001		74.79 (49.75)	0.196*	0.196*
(≤ 80µmol/L)	78			81			
(< 80µmol/L)	22			19			
Alanine		387 (146)	0.014*		460 (173)	0.916	0.349*
(≤ 455µmol/L)	78			44			
(> 455µmol/L)	22			56			
Arginine		134 (120)	0.711*		113 (138)	0.289*	0.605*
(≤ 119µmol/L)	61			75			
(> 119µmol/L)	39			25			
Citrulline		529 (888)	0.015*		573 (883)	0.026*	0.460*
(≤ 36µmol/L)	33			31			
(> 36µmol/L)	67			69			
Glutamine		730 (201)	0.533		753 (333)	0.532	0.659
(≤ 700µmol/L)	50			44			
(> 700µmol/L)	50			56			

Sig tested by one sample wilcoxon Signed Rank Test at p<0.05.
p-valuetestedwilcoxonsigned rank test at p< 0.05.

3.3. Biochemical Assessment

Table 3 compared mean of those biochemical parameters (total protein, albumin, ammonia, alanine, arginine, citrulline, and glutamine) against their reference value in each visit as well as between visits. In general, mean of all plasma amino acid profile shows no significant ($p>0.05$) differences between baseline and follow up visits, except total protein and albumin. These two biochemical indices were statistical significantly lower ($p < 0.05$) during follow up visit (66.01 ± 6.73, 39.71 ± 4.94g/L), nonetheless, when compared the figures from each visit against their reference value (≥ 66, ≥30g/L) respectively, mean of plasma albumin was significantly higher ($p < 0.05$) in both visits but total protein at first visit only.

Apart from liver profile, plasma ammonia and alanine level were significantly lower ($p< 0.05$) during the first visit (58.74±22.52, 387 ± 146 µmol/L) while no significant different ($p > 0.05$) shown at second visit (74.79 ± 49.75, 460 ± 173 µmol/L). On the other hand, plasma arginine and glutamine were all shown no significant different ($p > 0.05$) when compared against their reference value in both visits. Nevertheless, a noteworthy finding from the study was thatmajority of the children (67%, 69%) experienced significantly elevation of plasma citrulline during the both visits (529±888, 573±883 µmol/L) when compared against their target value which is ≤ 700µmol/L.

3.4. Clinical Profile

The incident percentage of each presenting sign and symptoms throughout these 10 months (March to end-December 2013) were shown in Figure 2. The most commonly incident of sign and symptoms observed was intellectual disability (44.4%), followed by poor appetite (22.2%) to hyperammonemia (16.7%). Lethargic, hypokalemia, and vomiting were each reported in 5.6% total of eighteen UCD children.

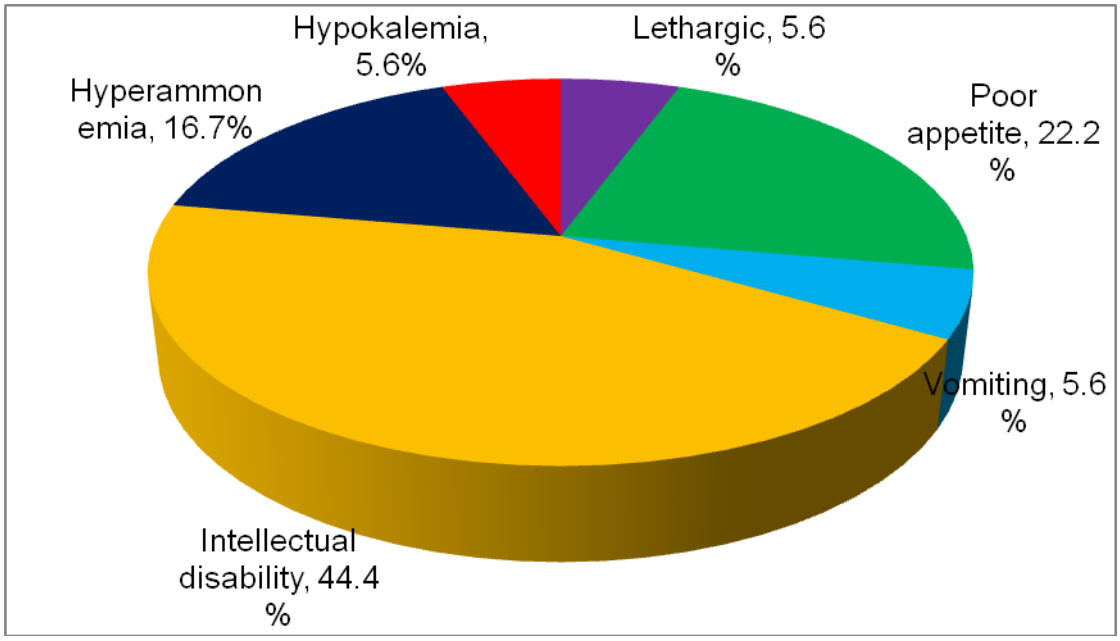

Figure 2. Incident (n=18) percentage of each observed presenting sign and symptoms during the both visits

3.5. Dietary Intakes

Table 4 displayed comparison mean percentage adequacy of macro and micronutrients according to Malaysian RNI (NCCFNM, 2005) between baseline and follow up. As a whole, there were no significant differences ($p>0.05$) of all nutrients between baseline and follow up regardless the combination of natural and medical food or relied solely on natural food or medical food except retinol, niacin, and ascorbic acid. The mean percentage adequacy of these three particular nutrients (retinol, niacin, and ascorbic acid) were statistical significantly lower ($p<0.05$) at follow up visit (40.67 ± 30.89µg, 16.95 ± 11.49mg, 109.56 ± 81.10mg) when compared against baseline study (65.76 ± 54.68µg, 19.20 ± 12.11mg, 179.25 ± 160.84mg).

3.6. Macronutrients

On average, UCD children (n=18) managed to achieve all recommended amount intake (> 100 % RNI) for all the macronutrients by daily natural and medical food consumption (106–124%) during the both visit except for protein (baseline: 87±36%, 21.47±9.03 g; follow up: 88±33%, 21.39±7.97 g). Natural food contributed with a minimum of 36 to 48% whereas supplement contributed at least 60 to 82% among UCD children in the context of macronutrient. In contrast, protein contributed from natural food resource was about 36–38% (9–10 g) while protein consumed from medical food recorded at 50 to 51% (11.7–12g) during the both visit.

3.7. Vitamins

In the context of vitamins, UCD children (n=18) managed to achieve more than 200 % of recommended amount intake nearly for all vitamins by relied on daily natural and medical food consumption (200–451%). Natural food contributed with a minimum of 31 to 179 % whereas supplement contributed at least 159 to 412 % among UCD children. However, vitamin B3 and E need to be highlighted in this study where mean percentage

adequacy of niacin was lower than 30 % in both visit (19 ± 12; 17±11%) while vitamin E in follow up (23 ±21%) visit.

Table 4. Distribution of UCD children's macro and micronutrients (n:18)

Nutrients (Unit)	Baseline		Follow-up		p-value
	Mean of intake (±SD)	Mean % adequacy (±SD)	Mean of intake (±SD)	Mean % adequacy (±SD)	
MACRONUTRIENT					
Energy (kcal/ day)					
Natural Food	551.34 (339.51)	39.08 (19.69)	595.70 (359.60)	42.74 (22.93)	0.093
Medical Food	836.72 (305.52)	67.05 (35.14)	807.44 (317.94)	64.90 (36.53)	0.078
Natural and Medical Food consumption	1388.06 (271.89)	106.13 (33.66)	1403.14 (268.49)	107.64 (34.87)	0.875
Carbohydrates (g/ day)					
Natural Food	89.19 (54.90)	45.75 (21.71)	92.52 (59.02)	47.70 (24.06)	0.124
Medical Food	108.39 (43.07)	63.30 (35.80)	102.62 (47.60)	60.14 (38.33)	0.807
Natural and Medical Food consumption	197.58 (45.58)	109.05 (34.35)	195.14 (48.88)	107.84 (35.53)	0.657
Protein (g/ day)					
Natural Food	9.45 (6.42)	36.08 (20.27)	9.67 (6.03)	37.89 (21.83)	0.646
Medical Food	12.02 (5.57)	51.31 (27.57)	11.72 (4.19)	50.18 (22.67)	1.000
Natural and Medical Food consumption	21.47 (9.03)	87.39 (35.84)	21.39 (7.97)	88.07 (33.34)	0.959
Fat (g/ day)					
Natural Food	17.18 (12.54)	35.52 (24.77)	20.21 (14.60)	42.81 (32.61)	0.136
Medical Food	35.38 (15.52)	82.03 (42.69)	34.93 (15.25)	81.04 (42.21)	0.386
Natural and Medical Food consumption	52.56 (11.98)	117.55 (40.47)	55.14 (14.65)	123.85 (45.94)	0.203
MICRONUTRIENT: VITAMINS					
Vitamin A / Retinol (µg/ day)					
Natural Food	302.43 (246.06)	65.76 (54.68)	184.67 (138.71)	40.67 (30.89)	0.003*
Medical Food	734.22 (219.23)	162.82 (55.62)	715.54 (214.51)	158.91 (54.97)	0.136
Natural and Medical Food consumption	1036.65 (373.87)	228.58 (87.98)	900.21 (237.45)	199.58 (61.53)	0.055
Vitamin B1 / Thiamin (mg/day)					
Natural Food	0.26 (0.16)	39.28 (23.76)	0.27 (0.22)	42.66 (38.10)	0.916
Medical Food	2.68 (1.77)	411.82 (291.15)	2.60 (1.47)	399.30 (238.27)	0.916
Natural and Medical Food consumption	2.94 (1.78)	451.11 (293.92)	2.87 (1.52)	441.96 (252.28)	0.799
Vitamin B2 / Riboflavin (mg/day)					
Natural Food	0.255 (0.17)	39.31 (27.38)	0.23 (0.16)	36.46 (27.64)	0.334
Medical Food	1.82 (0.91)	281.43 (149.76)	1.77 (0.71)	272.40 (115.47)	0.239
Natural and Medical Food consumption	2.08 (0.98)	320.74 (166.20)	2.00 (0.74)	308.86 (128.99)	0.333
Vitamin B3 / Niacin (mg NE/day)					
Natural Food	1.754 (1.35)	19.20 (12.11)	1.49 (1.08)	16.95 (11.49)	0.031*
Medical Food	17.72 (8.03)	210.48 (114.64)	17.15 (6.61)	204.56 (100.77)	0.423
Natural and Medical Food consumption	19.74 (8.39)	229.68 (118.89)	18.64 (7.03)	221.51 (107.12)	0.241
Vitamin C / Ascorbic acid (mg/day)					
Natural Food	56.48 (48.42)	179.25 (160.84)	34.36 (23.73)	109.56 (81.10)	0.028*
Medical Food	91.87 (28.44)	293.83 (105.60)	89.69 (27.68)	287.16 (101.63)	0.346
Natural and Medical Food consumption	148.35 (61.59)	473.08 (219.22)	124.05 (34.56)	396.72 (134.52)	0.193
Vitamin D (µg/day)					
Medical Food	11.90 (4.13)	238.09 (82.69)	11.63 (4.27)	232.53 (85.43)	0.695
Vitamin E (mg/day)					
Natural Food	1.73 (1.32)	31.33 (24.19)	1.23 (1.08)	23.00 (21.21)	0.073
Medical Food	14.90 (6.44)	273.54 (131.08)	14.51 (5.71)	266.23 (114.49)	0.460
Natural and Medical Food consumption	16.63 (7.24)	304.87 (148.09)	15.74 (6.30)	289.23 (129.17)	0.203
MICRONUTRIENT: MINERALS					
Calcium (mg/day)					
Natural Food	118.86 (66.13)	19.35 (11.05)	101.21 (85.98)	16.76 (14.65)	0.139
Medical Food	1069.64 (414.27)	176.52 (75.01)	1037.35 (353.25)	171.57 (66.03)	0.552
Natural and Medical Food consumption	1188.50 (410.35)	195.87 (75.63)	1138.56 (346.80)	188.33 (66.93)	0.209
Iron (mg/day)					
Natural Food	6.04 (4.44)	82.99 (54.29)	5.04 (3.94)	72.11 (56.02)	0.410
Medical Food	15.96 (6.12)	238.94 (108.63)	15.47 (5.17)	231.53 (90.74)	0.754
Natural and Medical Food consumption	22.00 (7.89)	321.93 (131.72)	20.51 (6.28)	303.64 (110.92)	0.139
Folate (µg/day)					
Natural Food	22.29 (22.61)	10.72 (11.88)	22.79 (17.64)	10.34 (8.49)	0.477
Medical Food	352.98 (232.07)	161.62 (114.59)	340.63 (190.97)	156.19 (93.60)	0.556
Natural and Medical Food consumption	375.27 (241.40)	172.34 (119.89)	363.42 (198.79)	166.53 (97.58)	0.721
Iodine (µg/day)					
Medical Food	111.25 (72.62)	112.18 (78.31)	107.34 (65.25)	108.83 (73.76)	0.345
Zinc (mg/day)					
Natural Food	1.48 (1.12)	26.98 (19.35)	1.42 (1.02)	25.76 (16.93)	0.379
Medical Food	14.47 (6.35)	283.90 (136.31)	14.04 (5.23)	276.42 (117.66)	0.386
Natural and Medical Food consumption	15.95 (6.46)	310.88 (136.70)	15.46 (5.29)	302.18 (116.89)	0.445
Selenium (µg/day)					
Natural Food	6.37 (3.48)	30.24 (16.74)	7.17 (4.53)	33.63 (20.97)	0.066
Medical Food	31.50 (14.82)	154.30 (79.75)	30.67 (12.54)	150.72 (71.53)	1.000
Natural and Medical Food consumption	37.87 (15.12)	184.54 (79.43)	37.84 (13.95)	184.35 (74.68)	0.722

p value tested by Wilcoxon Signed Rank Test at $p<0.05$.

3.8. Minerals

Apart from vitamins and macronutrients, result showed that UCD children afforded to achieve at least 167–322 % of recommended mineral intake by natural and medical food. The daily natural food intake contributed at least 30 to 83% while supplementation contributed the most from a minimum of 109 to 284%. However, result illustrated the mean percentage adequacy of calcium (19±11; 17±15%), folate (11±12; 10 ± 8%) and zinc (27±19; 26±17%) from daily natural food resource were clearly lower than 30 % in each visit.

4. Discussion

4.1. Characteristic and Socio-demographic Profile

The baseline characteristics (Table 4.1) of the study population revealed that the UCD cases was found to occur predominantly in female (61%), comparable to a study from Melbourne, where the majority of the cases also involved female group (Gardeitchik et al, 2012). According to a recent update by Weiner et al (2012), near of all UCD are inherited in an autosomal recessive manner; thus, it affects both boys and girls equally except for ornithine transcarbamylase deficiency (OTC) which is X-linked dominant; this particular disorder will usually show higher expressivity in female if the transmission is from father to child. Majority (94%) of the children were Malay which is similar to a previous local study from Institute Medical Research (Chen et al, 2010), where also the majority of the argininosuccinicaciduria cases were Malay (85%). Yet, there is no genetic study that could explain the possible reason about the higher prevalence of UCD among Malay. Next, Argininosuccinase acid lyaseDefiency (ASA/ASL) (22.2%), Argininosuccinic acid synthetase Deficiency (CTI/ASD) (22.2%), and Arginase Deficiency (AD/ARGD) (22.2%) were the most frequent types of UCDs diagnosed in this study. OTC, by contrast, was considered to be the most common urea cycle disorder in European countries (Adam et al, 2013) and Japan (Kido et al, 2012). Other noteworthy findings were that parental consanguinity was 1/3 of the cases and 99.4% of the cases were not associated with family history. These findings are in line with the study reported by Chen et al (2010), where parental consanguinity was commonly seen in inborn disorder. Nevertheless, there was one case (0.6%) whereby first degree family history of UCD was found which did not associate with parental consanguinity.Further genetic study should be explored regard the association between UCD and parental consangunity as well as family history.

Another interesting finding was that UCD children in this study were given breastfeeding on demand for an average of 20.11±52.02 days before it was stopped due to acute metabolic episodes. It is well recognised that breast milk not only provides complete nutrition, offers immunological benefits, consists of lower protein and amino acid content, but also reduce treatment cost for infants with inborn errors of metabolism (IEMs) (Leonard et al, 2002). In addition, a recent guideline for the management of urea cycle disorders (Haberle et al, 2012) suggested that main protein source for infants should be breastfeeding and exclusive breastfeeding is always possible. Nevertheless, it still remains a controversy nowadays because Huner et al (2005) highlighted that the feasibility of breastfeeding with UCD infants requires a very close monitoring with clinical parameters such as growth, development, biochemistry, including amino acids, organic acids and ammonia which might be a big challenge for physicians. Although they tried to document the clinical experience of breastfeeding of UCD infants (OTC-deficiency) in their study, the result indicated that breastfeeding was stopped due to poor metabolic control and insufficiency of breast milk. Besides, other difficulties might be encountered during breastfeeding process such as potential risk of catabolism, protein requirement change in particular with severity of disease, education on breast milk pumping (Huner et al, 2005), varying amino acid content in breast milk for the first 12 months of lactation period (Nommsen, 1991), and the need for close supervision in calculating the protein content of breast milk to allow this changeover from breastfeeding to bottle feeding (Haberle et al, 2012). To date, no study has yet documented any successful clinical experience of breastfeeding among UCD infants. Therefore, exclusive breastfeeding is not commonly seen and practised in Malaysia. Next, the income status (EPU, 2010) demonstrated that majority (50%) of the children of the children came from families with low income and the mean of monthly feeding budget were approximately RM519.44 ± 229.54.

4.2. Anthropometry Measures

The prevalence of malnutrition between baseline and follow up based on anthropometric measurements was 66.6%, 60.4%stunted and 44.4%, 29.5% underweight. Approximately 33.3% showed microcephalic for head circumference-for–age criterion. However, the prevalence of stunting (height-for-age) among this category of children was lower in a previous local study among 24 IEMs children in HKL (33% and 29%) as reported by Mansooret al(2010). In fact, there were only 50% (12/24) of MSUD children accounted in her study. Similarly, an intervention study conducted in multiple medical centres of USA (Acosta et al, 2005) also reported that there were only 18% (3/17) of UCD children (0–4 years old) having stunted growth during the baseline study. Again, the reported mean z-score (−1.2±0.3 SD) is also higher than our data. Nevertheless, there are some case studies (Prasad et al, 1997; Brockstedt et al, 1990) showed agreement with our finding, where exceedingly poor height growth in children with arginase deficiency was reported.Apart from the finding of height-for-age, prevalence of underweight (weight-for-age) in this study was much higher compared to the figures (21% and 16%) reported by Mansooret al(2003). Next, as regard to head circumference-for-age, the findings of the present study revealed that UCD children were averagely classified under category of microcephaly (< -2 SD) based on the mean z-score of head circumference in both visits (−2.41 ±1.82 and −2.35±1.78cm) despite only minority (33.3%) of the UCD children were each registered at values ≤−2SD (microcephaly) in both visit. In contrast, the finding from Acosta et al (2005) demonstrated that all of their recruited

UCD children (n = 17) had normal head circumference (HC) (mean −2 to <0 SD) during the baseline (−0.9±0.3 SD) and follow-up (−0.4±0.3 SD) visits. Based on the medical records, UCD children had never been diagnosed as being microcephalic and for this reason, the aetiologies remain unknown. In fact, a normal HC (±2SD) only showed that the children are statistically normal, but it still does not explain the cause-and-effect relationship between the head circumference and the brain development or intelligence(Ivanovic et al, 2004). Further research should be carried out in this regard.

4.3. Biochemical Assessment

4.3.1. Albumin and Total Protein

Plasma albumin and total protein concentration are considered as classic parameters of nutritional status (Cooper etal, 1993; Rombeau et al, 2001). The findings from this study revealed that the mean of plasma total protein and albumin concentration among 18 UCD children were significantly higher than the reference concentration (≥ 66; 30 g/L) at baseline (70.7±5.1; 42.5±4.3 g/L) while during follow up only albumin showed higher value (39.7±4.9 g/L) but total protein (66.0±6.7 g/L) did not attain any significant difference against the standard value. Besides, figure of percentage also shows that none of them were having albumin level below recommended value. This finding was in line with a cross-sectional multicentre study (Tuchman et al, 2008) conducted in USA, where they found that 165 UCD children, who were then receiving medical and diet therapy at their respective centre, had attained total protein (69.5 g/L) and albumin concentration (40.5 g/L) required. Acosta et al (2005) also showed agreement with this finding where 53% of UCD children (9/17) in their study achieved above reference value of albumin (34 g/L) at baseline level. In spite on the fact that various studies have shown that low blood levels of albumin can indicate a poor prognosis, malnutrition, mortality (Harvey et al, 1981), longer periods of hospitalisation and a higher risk of hospital readmission (Herrmann et al, 1992), the target population from these well structured studies were mostly referred to adult population. To date, we have not found any references in the literature related to validity and the practicality of using total protein and albumin to indicate risk of malnutrition among UCD children. Besides, Huhmann & Cunningham (2005) reported that serum albumin was not a sensitive indicator of nutritional status as it had a 14-to 20-day half-life and broad distribution (synthesis, degradation, losses, and redistribution within the body compartments) in the body that prevent nutritional changes from being rapidly reflected in plasma albumin concentration. Therefore, serum albumin does not clearly reflect the nutritional status among children with UCD.

4.3.2. Ammonia

Generally, hyperammonemia is toxic to the central nervous system (CNS), which can provoke severe neuropsychiatric disorder named hepatic encephalopathy, altered mental status and coma (Braissant, 2010). The underlying reason is because the brain is unable to convert NH4+ to urea due to its lack of urea cycle enzymes (Cagnon, 2007). Unfortunately, paediatric population is much more susceptible to the deleterious effects of NH4+ compared to adult; most of the time, the CNS damage is irreversible (Cagnon, 2007). Therefore, monitoring of ammonia level is extremely important to prevent metabolic episodes, death and any CNS complications. In the present study, the result revealed that ammonia level among 18 UCD children during baseline (59±23 µmol/L) and follow-up (75±50 µmol/L) study were categorised under normal reference value (≤ 80 µmol/L). In fact, it was significantly lower ($p < 0.05$) during baseline study. This finding was in line with a recent study (Serrano et al, 2011); where they found ammonia level among 26 UCD children who were receiving treatment was also significantly lower (73±80 µmol/L).

4.3.3. Alanine

Alanine concentration reported in this study showed a good outcome during this 10-month study. No significant difference on plasma alanine concentration against the reference value (≤ 455 µmol/l) in follow up visit as well as between visits, except it was significantly lower during baseline study. It was recorded at 387±146 µmol/l and 460±173 µmol/l during baseline and follow-up visits, respectively, comparable with the finding from Tuchman et al (2008), where they also found that alanine concentration (401 µmol/L) among 165 UCD children were below the reference value.

4.3.4. Arginine

Similar to the result of alanine, arginine concentration reported in this study was under acceptable range as it showed no significant difference against the reference value (≤ 119 µmol/L) in each visit (134 ± 120; 113 ± 138 µmol/L) as well as between the both visits. This finding was coherent with a recent cross-sectional study (Tuchman et al, 2008), where they found that arginine concentration (94 µmol/L) among 165 UCD children were below the reference value. Indeed, adequacy of plasma arginine level is extremely crucial to ensure the balance of nitric oxide (NO) synthesis (precursor for nitric oxide) and avoid cerebral energy deficit (creatine synthesis) (Braissant, 2007). NO is important in modulating cerebral processes especially intercellular communication through glutamate-NO-cGMP pathway by activating soluble guanylate cyclase which resulting in increased concentration of cGMP (Cagnon, 2007). On the other hand, excessive elevation of NO concentrations can interact with superoxide anion, leading to the formation of the highly toxic peroxynitrites in the neighbouring neurons, which then leads to neuronal death (Braissant, 2010). Moreover, it has been suggested that NH4+-induced production of NO could inhibit glutanate synthase (GS), the only NH4+ detoxification pathway in the brain, which might worsen the consequences of hyperammonemia on CNS (Rose, 2005). Next, the creatine/phosphocreatine/creatine kinase system is essential for the buffering and transport of high-energy phosphates (Wyss, 2000), and the mammalian brain is able to perform its own creatine synthesis during adequacy of arginine concentration in order to avoid suppressing of TCA cycle which could possibly induce neuronal death (Braissant, 2007).

4.3.5. Citrulline

On average, plasma concentration of citrulline reported at higher level significantly compared with the reference value (≤ 36 µmol/L) in both visits. It was recorded at 529±888 µmol/L and 573±883 µmol/L during baseline and follow-up visits, respectively. This finding was verified by the study of Tuchman et al (2008), where an average of 499 µmol/L of plasma citrulline level among UCD children was reported. They also found that citrulline was commonly extremely high only in the UCD subtype of argininosuccinatesynthetase (citrullinemia) (1685±1325 µmol/L) and relatively high in argininosuccinatelyase (184 ± 90 µmol/L) despite regular diet and medical therapy. Therefore, a further investigation from our study indicated that citrulline level were significantly ($p<0.05$) high in argininosuccinatesynthetase (ASS) (baseline: 2075.25±589; follow-up: 2029.25±304 µmol/L), followed by argininosuccinatelyase (ASL) (baseline: 196.25±31; follow-up: 228±67 µmol/L). Other subtypes of UCD only contributed insignificant ($p>0.05$) plasma concentration of citrulline during baseline (49.25±46 µmol/L) and follow-up (45±42 µmol/L). In view of these results, regular monitoring of citrulline level in UCD subtype of ASS and ASL is more crucial as they possessed at a higher risk of cerebral energy deficit and imbalanced citrulline-nitric oxide cycle due to high plasma level of citrulline (Gregory, 2008).

4.3.6. Glutamine

Glutamine is considered an organic osmolyte result from incorporation of glutamate with ammonia via glutamine synthetase (GS) localised to the astrocyte in the brain (Gregory, 2008). This reaction is crucial as a short-term buffering of excess plasma ammonium system. Nevertheless, in the past two decades, various studies concluded that hyperammonemic conditions which consistently associated with an increase of brain glutamine, at least, 2- to 3-fold (Connelly et al, 1993; Inoue et al, 1987) can lead to encytotoxic cerebral edema by allowing entry of water into astrocyte (collectively name as astroglia or brain cell) (Cagnon, 2008). Therefore, monitoring of plasma glutamine level in UCD children is to prevent the occurrence of cerebral edema as well as hyperammonemia. In the present study, a positive outcome (≤700 µmol/L) has been observed in biochemical indices of plasma glutamine concentration among 18 UCD children during baseline (730±201 µmol/L) and follow-up (753±333 µmol/L) period. Both showed no significant difference against the reference value (≤ 455 µmol/l) in each visit as well as between both visits. The findings are parallel to the study of Tuchman et al (2008) and Serrano et al (2011), where they reported that the mean plasma glutamine concentration remained lower (689; 775±337 µmol/L) than the reference range among UCD children (n =165; n =26) who were then receiving diet and medical therapy at the same time. Nevertheless, based on the categorical figure, there is quite a number (50%; 56%) of children having mean plasma glutamine above recommended value during both visits. For this reason, a further exploration using non parametric statistical method was carried out. However, result from this particular finding indicated there is no significant median difference ($p>0.05$) of plasma glutamine level between different subtypes of UCD, regardless baseline ($p=0.108$) or follow up ($p=0.06$) visit.

4.3.7. Clinical Profiles

Intellectual disability was the most common symptoms (44%) observed among children surviving with inborn errors of urea cycle during this 10-month study. This finding was in line with a few studies (Cagnon, 2007; Gregory, 2008) where majority of surviving UCD children were reported to experience the same problem. Intellectual disability is a life-long and debilitating condition with deficits in cognitive function (IQ < 70) (Clara et al, 2012). Indeed, intellectual disability (ID) is also known as global developmental delay and mental retardation. Global development delay applies to age < 5 years old whereas mental retardation applies to ≥ 5 years (Shevell, 2008). In this study, ID was used collectively for both ID and DD (developmental delay). It frequently happens on late onset hyperammonemia neonate and infants due to failure detection of hyperammonemia or immediate removal of ammonia (Gonzalec et al, 2010; Takanashi et al, 2003b). In spite of the fact that a study indicated that children with later onset of hyperammonemia may have a normal neurodevelopment if the diagnosis is made before they sustain an irreversible cerebral insult (Kurihara et al, 2003). The exact aetiology remains unclear but brain MRI of surviving UCD children have indicated diffuse cortical atrophy and lesions in basal gangli, sometimes with cortical multicystic formations and appearance of myelination delay (Yamanouchi et al, 2002; Takanashi et al, 2003b). Furthermore, MRI observation of brain lesions within the first few days of life suggested that some of these lesions or defects of development due to urea cycle diseases might be already acquired *in utero* (Majoie et al, 2004). Nevertheless, an early screening among high risk group should be encouraged to sustain any possibility of not having problem of intellectual disability.

Other symptoms presented were poor appetite (22%), hyperammonemia (17%), lethargy (6%) and vomiting (6%). Gardeitchik et al (2012) also reported that frequent vomiting and poor appetite are the common eating behaviour after UCD diagnosis. According to Acosta et al (2005), these symptoms are usually precipitated by protein intake beyond what the UCD children can metabolise or by catabolism of lean body mass resulting from intercurrent infection, trauma, inadequate protein or essential amino acid intake.

Lastly, there were approximately 6% of incident found with experiencing problem of hypokalemia. The precipitating factor recorded was secondary to sodium benzoate. Sodium benzoate is commonly used to eliminate plasma ammonia by alternative liver enzyme pathways; benzoate is conjugated with glycine to form hippurate, which is then eliminated in urine (Myers et al, 1996). However, these actions will no doubt enhance up to at least five fold of normal glomerular filtration rate which might increase excretion of potassium in urine (Batshaw, 2001). Therefore, sodium benzoate is likely to induce hypokalemia among surviving UCD children.

4.3.8. Nutrients Intakes

By far, this is the only study across the worldwide which evaluating the dietary intake of MSUD children from three different aspects as follow: natural food,

medical food and combination of natural and medical food consumption. The main finding from the dietary aspect was that UCD children in this study were not at risk for any macro and micronutrient deficiencies by judging figures (106.13±33.66–451.11±293.92% of RNI) reported from the combination of daily natural and medical food consumption. Medical food (50.18±22.67–179.25 ± 160.84%) will be required in all cases as children were not able to meet RNI by solely depending on natural food intake (10.34±8.49–126.6±151.8%).Result also indicated UCD children tend to achieve significant lower during follow up visit in those particular nutrients from natural food sources such as vitamin A (p=0.003), vitamin B3 (p=0.031) and vitamin C (p=0.028). Besides, they also prone to achieve less than 30% of RNI in particular micronutrients such as vitamin B3, vitamin E (follow up visit only), calcium, folate, zinc if solely depending on natural food consumption.

4.4. Macronutrients

The intake of macronutrients (energy, carbohydrate, fat) from natural and medical foods (106–124% RNI) (NCCFNM, 2005) by UCD children indicated that an adequate supply of protein-free energy is important not only to prevent catabolism which can increase the production of ammonia but also to support anabolism (Cagnon, 2007). This finding clearly showed agreement from a recent UCD management protocol published by Singh (2007). Next, an interesting highlighted point noted from the result was that total protein intake contributed from both resources was between 87–88% (21–21.5 g) of RNI (NCCFNM, 2005), however by comparing according to Ross et al (2005), the suggested nutrition guideline for UCD children, it was around 100–102%. Nevertheless, the mainstay of long-term management should always be individually determined and most accuracy is by titration against ammonia level (Häberle, 2012). In fact, this deviation indicated that protein intake among UCD children was lower than the normal healthy children, by at least 12%. Surprisingly, when we breakdown the protein prescription, it was found that natural food contributed about indeed contributed about 42.9–46.1% (9–10 g) whereas the medical food recorded at 53.9–57.1% (11.7–12 g) by calculating at 100%. This finding, indeed, is still in line with the arbitrary recommendation by Urea Cycle Disorder Conference Group (2001) that at least 50% protein intakes should be given as essential amino acid mixtures (medical food) to reduce waste nitrogen from endogenous and exogenous sources. However, this practice is markedly different when compared to a UK cross-sectional study (Champion, 2012) from 16 IMD (inborn metabolic disorders) centres where patients with severe defects are only given 50% of the protein prescription from medical food, in fact, only 30% of patients were only prescribed medical food between 20–30% of total protein intake, which is absolute lower than our findings (53.9–57.1%). Moreover, a recent UCD guideline also highlighted that a reasonable approach is to provide only 20–30% of total protein intake as EAA supplements or medical food (classified with recommended level of evidence grade C) (Häberle, 2012). The theoretical advantages of replacing natural protein with medical food are to provide a high-quality protein equivalent and thus reducing the nitrogen load to the urea cycle, by giving less non-EAAs (Champion, 2012). Besides, a past study conducted also showed that nitrogen content from medical food (8.5–13.7%) was lower than the nitrogen content in natural food (13.4–19.1%)(Chang, 2010). Another further theoretical advantage is that circulating ammonia is used in the recycling of EAAs to form non-EAAs (Singh, 2010).

4.5. Vitamins

The children in this study were able to achieve at least 200–451% RNI (NCCFNM, 2005) of all vitamins from the total of both resources and clearly, they are not at risk for any vitamin deficiency. However, Vitamin A, C, and B3 from natural food resource was significantly lower ($p < 0.05$) in the follow-up visit (41 ± 31%; 110 ± 81%; 16.95 ± 11.49). Besides, vitamin B3 and E need to be highlighted in this study where mean percentage adequacy of niacin was lower than 30% in both visits (19±12%; 17±11%) while mean percentage adequacy of vitamin E was lower in the follow-up (23±21%) visit. This finding is somehow supported by Dixon (2007) where majority of UCD patients on low protein diet could be at risk of vitamin deficiencies.

4.6. Minerals

Minerals intakes as a percentage of RNI in UCD children were approximately 167 to 322%. Similar from the vitamin, the major contribution was also from medical food resource (109–284%). Despite mineral deficiency not existed in our finding, yet UCD children' natural food intake of calcium (19±11%; 17±15%), folate (11±12%; 10±8%)and zinc (27±19%; 26±17%) were found to be less than 30%. This finding was in line with a study conducted by Dixon (2007) where majority of UCD patients on low protein diet are reported to be at risk of mineral deficiencies, in particular calcium and zinc. According to Tee et al (1997), the generally lower intake of this particular minerals could be due limited food choices as these nutrients food resources mainly come from rich protein food such as milk, dairy products, fish, anchovies, legumes, bean products and sea foods which they might need to restrict from their daily dietary intake to prevent elevation of plasma ammonia.

5. Conclusion

This study did not find significant differences in the nutritional status among a sample of children with UCD undergoing active regular diet and medical treatment. In view of anthropometry data, a prominence in growth stunted, undernutrition and microcephalic were suggested among UCD children. Besides, only the mean of plasma citrulline, albumin, total protein of our children in many cases was above reference value, however, the only parameter that require attention of physician was citrulline. Next, the top three most documented sign and symptoms were intellectual disability, poor appetite and hyperammonemia. Nevertheless, the study did not found intake of any macro and micronutrients that fall short of the recommended intake in both visits based on the figures reported from both resources, although intake of vitamin

A, B3, C were significant lower in follow visit and also intake of niacin, vitamin E (only during follow up visit), calcium, folate, zinc from natural food resource were below 30% of RNI.

Although a great deal of research and clinical experience has contributed to the understanding of the impact of disease on nutritional status of children with UCD as well as the formation of suggested guidelines and treatment protocols, much more longitudinal nutrition surveys in future are needed in order to have a clearer understanding on the effect of disease or treatment upon metabolism, growth and development among children with UCD.

5.1. Strengths and Limitations

The strength of this study is the large representative sample of the Malaysian UCD children from a wide range of socio-demographic backgrounds with follow up at 6 month interval. The limitation in the present study was to use a single 24-hour recall. Multiple 24-hour recalls would have provided better estimates of intake, but would have also increased respondent burden, which in turn may have contributed to decreased participation in this study notwithstanding the cost that it may have incurred. Finally, a limitation that cannot be overlooked in self-reported dietary intakes is that food and nutrient intakes are often under-estimated. Black & Cole (2001) estimated under-reporting in dietary assessment methods to be 64%, 88% and25% of the results using diet records, diet recall and diet history, respectively. Yet, this study utilised well-trained dietitian and the interactive approach in which repeated and skilful probing was done to help the respondents recall as accurately as possible all food and fluids consumed.

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Compliance with Ethic Guidelines.

Conflict of Interest Statement

Authors declare that they have no conflicts interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients included in the study and available upon request. If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. Additional informed consent was obtained from all patients for whole identifying information is included in this article.

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