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Original research article

The effects of low protein products availability on growth parameters and metabolic control in selected amino acid metabolism disorders patients

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ABSTRACT

Background: In Saudi Arabia, a diet for life policy has been adopted in the management of amino acid metabolism disorders for years. However, the specially designed low protein products/medical foods - which are one of the important treatment tools - were not available up until several years ago in Saudi Arabia (SA). Our aim was to measure the compliance and quality of life in patients affected with these disorders followed in the metabolic nutrition clinic at King Faisal Specialist Hospital & Research Centre (KFSH&RC), Riyadh, SA.

Methodology: We used a non-randomized retrospective/prospective study which utilized the growth parameters, biochemical data of patients plus questionnaires collected from patients and their family/caregivers. A total of n = 182 patients affected with selected amino acid metabolism disorders were enrolled. Some were excluded n = 84 for various reasons. Sample analyzed were: Phenylketonuria (PKU) (44), Maple Syrup Urine Disease (MSUD) (30), Tyrosinemia (TYR) (17) and Homocystinuria (HCU) (7). Tandem Mass Spectrometry (TMS) used to quantitate plasma amino acid concentrations. Data was obtained using (COMPLE) Microsoft-Access which was designed by the metabolic nutrition clinic at KFSH&RC-Riyadh. Student's paired *t*-test was used to investigate relationship between variables.

Results: The main findings were the improvement of selected amino acid levels pre and post the usage of medical foods. In PKU patients, the TMS Phenylalanine (PHE) levels post usage was significantly decreased (*P* value < .0001). This was also the case in MSUD patients with significant decrease in Leucine & Isoleucine levels (*P* value .0008) but not in Valine levels (*P* value .1148) as 36.7% of them received Valine supplements while enrolled in the study.

Conclusion: Low protein products availability was successful in improving outcomes for selected amino acid metabolic disorders. However, due to compliance issues and impracticality of the diet, the results were not significant in all enrolled patients.

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1. Introduction

Disorders of protein and amino acid metabolism: Phenylketonuria (PKU), Maple Syrup Urine Disease (MSUD), Tyrosinemia (TYR), Homocystinuria (HCU) and Organic Acidemias (OA) are a class of inherited metabolic conditions that occur when certain amino acids either cannot be broken down or produced by the body, resulting in toxic accumulation of some substances and/or the deficiency of others. While Urea Cycle Disorder (UCD) defined as a genetic disorder caused by urea cycle enzymes deficiencies that result in waste nitrogen accumulating as ammonia and glutamine which are neurotoxin. These disorders are managed by life-long diet restriction. The aims of nutrition therapy in these disorders are: (a) reducing the production of toxic substances by restricting the offended nutrient in the patient's diet, (b) providing adequate calories, protein, vitamins and minerals which are necessary for optimal growth and development. To achieve this, amino acid metabolism disorders diet consists of:(a) synthetic amino-acid based formula,(b) calculated and measured amount of natural protein source, (c) carbohydrates and/or fat polymers are added to diet to build up calories and prevent catabolism, (d) specific calculated amino acid supplement as needed, (e) specially designed low protein foods/products. An individual approach combining all of the above will help in achieving expected outcomes. Specially designed low protein foods are products (i.e. low-protein pasta, rice, flour and bread) formulated to have $\leq$1 g protein per serving which are expected to provide 50–75% of estimated daily energy needs in patients with amino acid metabolism disorders [1]. For this reason patients are likely to need a large quantity and variety of products on an ongoing basis. They are substantially more expensive than regular food [2,3], and not readily available to purchase.

For patients with inherited metabolic disorder (IMD) the capacity to adhere to dietary restriction and overall management depends on both the patients and their caregivers [4]. Not adhering to the dietary restriction usually starts at school age (5–6 year old), leading to very poor compliance as children grow older (10–15 year old) [3,5–8]. Reasons may be due to lack of dietary variation, cost and unavailability of specially designed low protein products/ medical foods [9]. Additionally, feeding difficulties were common in children with IMD as reported in the literature [10,11]. It is also a dynamic process, with many patients varying in their levels of acceptance and willingness to adapt to such a strict diet or be selective in the adherence [4,12]. In addition to diet restriction, patients and caregivers usually complain about the frequent laboratory tests. It is also common that adult patients would improve their compliance just before lab test to ensure better results [3,8]. Furthermore, some of the amino acid metabolism disorders pose no risks of acute crisis e.g. PKU, HCU and TYR. While other disorders such as UCD, MSUD and OA could lead to frequent hospital admissions due to metabolic crisis secondary to poor dietary adherence [13]. Frequent admissions subsequently will negatively affect dietary adherence. As stated in the WHO report of adherence to long term therapies, compliance defined as (the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider) [12,14,15]. Therefore, no clear measurement of compliance has been defined [4]. The degree of dietary control required in these cases remains a controversial topic. However, from our practice, it is impossible to state that dietary liberalization is completely safe, equally it is futile to continue a strict dietary approach if our patients are refusing such a regimen.

Worldwide, a lot of research is done in regards to diet in the treatment of PKU which is the most common amino acid metabolism disorder in USA and UK. Most of these state a significant beneficial effect of phenylalanine restricted diet on intellectual achievement, neurologic status and behavioral improvement [8,16–19]. However it could have a negative effect on physical growth [20,21] and an enhanced quality of life for both the patients and their caregivers in early and even late diagnosed patients [22]. Moreover, health related quality of life was reported to be compromised in IMD patients, which leads to increased demands of emotional and psychosocial support [23]. Most of the studies involved PKU patients with few papers published on other protein and amino acids metabolism disorders.

Growth parameter for these patients is usually compromised due to dietary restriction [24,25]. Lack of international publications related to growth and development of such patients impedes the comparison process. Vitamins and minerals deficiencies were reported in those groups of patients which can rapidly impair growth [7,26]. That could be due to the insufficient adherence to the synthetic amino-acid based formula provided or as consequences of the multiple dietary modifications that may place the patients at risk of macro and micronutrient deficiency [27,28]. Zinc, selenium, vitamin B12 and other deficiencies were reported long time ago mainly in PKU patients and other IMD [17,20,29–36].

Saudi Arabia is one of the pioneers in treating patients affected with IMD around the world due to the high prevalence of these diseases (almost 4 times higher incidence than in USA) as per the Saudi national lab newborn screening program database [37,38]. This is related to our society's high rate of consanguinity and inter-caste marriages.

Dietary management is crucial for these patients through well trained metabolic dietitians which are unfortunately scarce in the rural areas of Saudi Arabia. Thus, such cases are referred to KFSH&RC-Riyadh from all over the Middle East, adding to the importance of this study.

2. Method

2.1. Study design

This is a non-randomized, retrospective/prospective study. Data before medical foods usage was retrospectively collected while post usage was prospectively gathered. Data were collected over around 2.6 year period, using (COMPLE) Microsoft access which was designed by the metabolic nutrition clinic at KFSH&RC-Riyadh. A written questionnaire was developed for this study. It was written in Arabic and also available in English, translated from Arabic to English by a professional translator. Questionnaire was validated through 3 well-educated mothers with affected patient/s, 4 clinical dietitians and 2 medical genetic physicians. It was developed covering socio-demographic data and technical challenges, and addressing the following topics: (a) compliance to dietary management and biochemical work-up from the view of patients and caregivers, (b) difficulties in choosing the appropriate food while following the restricted diet, (c) social life and academic performance, and (d) palatability and preparation of medical foods.

The study was conducted in accordance with the ethical principles contained in the Declaration of Helsinki (2000), the ICH Harmonized Tripartite Good Clinical Practice Guidelines, the policies and guidelines of the Research Advisory Council of KFSH&RC, and the laws of Saudi Arabia. A verbal informed consent was taken from the patients caregivers.

2.2. Participants

Inclusion criteria included (a) patients 2 years old and above, (b) affected with one of the selected amino acid metabolism disorders, (c) following up in the metabolic nutrition clinics at KFSH&RC-