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Dietary management of urea cycle disorders: European practice

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ABSTRACT

Background: There is no published data comparing dietary management of urea cycle disorders (UCD) in different countries.
Methods: Cross-sectional data from 41 European Inherited Metabolic Disorder (IMD) centres (17 UK, 6 France, 5 Germany, 4 Belgium, 4 Portugal, 2 Netherlands, 1 Denmark, 1 Italy, 1 Sweden) was collected by questionnaire describing management of patients with UCD on prescribed protein restricted diets.
Results: Data for 464 patients: N-acetylglutamate synthase (NAGS) deficiency, n = 10; carbamoyl phosphate synthetase (CPS1) deficiency, n = 29; ornithine transcarbamoylase (OTC) deficiency, n = 214; citrullinaemia, n = 108; argininosuccinic aciduria (ASA), n = 80; arginase deficiency, n = 23 was reported. The majority of patients (70%; n = 327) were aged 0–16 y and 30% (n = 137) >16 y. Prescribed median protein intake/kg body weight decreased with age with little variation between disorders. The UK tended to give more total protein than other European countries particularly in infancy. Supplements of essential amino acids (EAA) were prescribed for 38% [n = 174] of the patients overall, but were given more commonly in arginase deficiency (74%), CPS (48%) and citrullinaemia (46%). Patients in Germany (64%), Portugal (67%) and Sweden (100%) were the most frequent users of EAA. Only 18% [n = 84] of patients were prescribed tube feeds, most commonly for CPS (41%); and 21% [n = 97] were prescribed oral energy supplements.
Conclusions: Dietary treatment for UCD varies significantly between different conditions, and between and within European IMD centres. Further studies examining the outcome of treatment compared with the type of dietary therapy and nutritional support received are required.

1. Introduction

Urea cycle disorders (UCD) are rare defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen containing molecules. Partial deficiency or total absence of activity of any of the enzymes in the urea cycle (including carbamoyl-phosphate synthetase 1 [CPS1], ornithine transcarbamoylase [OTC], argininosuccinate synthetase [ASS], argininosuccinate lyase [ASL], arginase or the co-factor producer, N-acetylglutamate synthase [NAGS] results in the accumulation of ammonia and other metabolites. The resulting hyperammonaemia, manifested by a variety of symptoms including central nervous system dysfunction, is associated with high mortality [1] and morbidity [2]. Although symptoms mainly develop in the neonatal period, patients differ in presentation age, the character and severity of symptoms and in their susceptibility to metabolic derangement depending on the affected enzyme and its residual activity [3]. Dietary treatment for UCD involves reducing both endogenous and exogenous waste nitrogen by limiting dietary protein intake and providing adequate protein-free energy to minimise protein catabolism. In addition, nitrogen scavenging drugs are frequently used to control these patients [4,5].

The maintenance dietary treatment of UCD is based on the provision of a diet low in natural protein, supplements of essential amino acids as indicated and appropriate nutritional support to avoid catabolic stress. There are few analytical studies to support the long term dietary treatment approach to UCD [5] and this appears to have developed by custom and practice. In the recently published UCD guidelines [5], most dietary recommendations were only based on Grade C–D (expert opinion and case reports/case series) evidence [5]. They suggest that the FAO/WHO/UNU safe levels of protein [6] be used as a guide to protein requirements and a pragmatic recommendation of 20–30% of total protein from EAA supplements (as clinically indicated) with the exception of arginase deficiency. It is unknown how European dietary management of UCD compares with these dietary guidelines.

This paper aims to describe and compare dietary practices in UCD from a number of different IMD centres throughout Europe caring for both children and adults with UCD. It compares practice within and between countries.

2. Materials and methods

2.1. Study design

Members of the Dietitian's Group of both the Society for the Study of Inborn Errors of Metabolism (SSIEM) and the British Inherited Metabolic Disease Group (BIMDG) representing hospitals treating patients with IMD throughout Europe were sent a questionnaire (consisting of 40 open and closed questions) about the dietary management of UCD in their centre. Dietitians were requested to cascade this questionnaire to other dietetic colleagues within their country.

Demographic and nutritional data were collected on prescribed diet therapy for current patients with UCD. Information on patients' dietary treatment whilst in a steady state (not catabolic or newly diagnosed) included: prescribed natural protein; supplements of EAA and branch chain amino acids (BCAA); use of enteral tube feeds and oral energy supplementation. The prescription of nitrogen scavenging drugs, L-arginine or L-citrulline, is not reported. Clinical outcome and biochemical data are also not described.

Ethical approval was not required for this study as no specific identifiable patient data was obtained or used. This was an audit of current practice in dietetic management of UCD.

3. Results

Questionnaires were returned from 9 countries, representing 41 IMD centres across Europe (Table 1), each centre had between 1 and 71 patients (median 8) providing data on 464 patients with UCD: N-acetylglutamate synthase (NAGS) deficiency, n = 10; carbamoyl phosphate synthetase (CPS) deficiency, n = 29; ornithine transcarbamoylase (OTC) deficiency, n = 214; citrullinaemia, n = 108; argininosuccinic aciduria (ASA), n = 80 and arginase deficiency, n = 23 (Table 1). There was variation in the percentage of each condition between reporting countries although OTC and citrullinaemia were the most common (Table 1). All UK data have been previously published [7].

3.1. Patient description

The age distribution of patients is given in Table 2. Forty-three percent (n = 200) of patients were diagnosed by 30 days of age. All patients were on prescribed protein restricted diets. The ethnic origin of most patients was white European (74%, n = 343) followed by Pakistani (9%, n = 44) (predominantly from the UK, n = 41) and Arabic (7%, n = 33) (predominantly from France, n = 16; and Germany, n = 13).

3.2. Protein intake

The prescribed median total protein intake per kg body weight decreased with age across all disorders (Figs. 1–5). Information on just

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