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Dietary practices in pyridoxine non-responsive homocystinuria: A European survey

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ABSTRACT

Background: Within Europe, the management of pyridoxine (B_6) non-responsive homocystinuria (HCU) may vary but there is limited knowledge about treatment practice.
Aim: A comparison of dietetic management practices of patients with B_6 non-responsive HCU in European centres.
Methods: A cross-sectional audit by questionnaire was completed by 29 inherited metabolic disorder (IMD) centres: (14 UK, 5 Germany, 3 Netherlands, 2 Switzerland, 2 Portugal, 1 France, 1 Norway, 1 Belgium).
Results: 181 patients (73% > 16 years of age) with HCU were identified. The majority (66%; n = 119) were on dietary treatment (1–10 years, 90%; 11–16 years, 82%; and > 16 years, 58%) with or without betaine and 34% (n = 62) were on betaine alone. The median natural protein intake (g/day) on diet only was, by age: 1–10 years, 12 g; 11–16 years, 11 g; and > 16 years, 45 g. With diet and betaine, median natural protein intake (g/day) by age was: 1–10 years, 13 g; 11–16 years, 20 g; and > 16 years, 38 g. Fifty-two percent (n = 15) of centres allocated natural protein by calculating

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methionine rather than a protein exchange system. A methionine-free L-amino acid supplement was prescribed for 86% of diet treated patients. Fifty-two percent of centres recommended cystine supplements for low plasma concentrations. Target treatment concentrations for homocystine/homocysteine (free/total) and frequency of biochemical monitoring varied.

Conclusion: In B_6 non-responsive HCU the prescription of dietary restriction by IMD centres declined with age, potentially associated with poor adherence in older patients. Inconsistencies in biochemical monitoring and treatment indicate the need for international consensus guidelines.

1. Introduction

Pyridoxine (B_6) non-responsive homocystinuria (HCU) is a multisystem disorder due to cystathionine-β-synthase (CBS; EC 4.2.1.22) deficiency. HCU causes increased plasma concentrations of homocysteine leading to accumulation of the amino acid methionine (MET) [1]. CBS deficiency also causes elevated concentration of S-adenosylmethionine and S-adenosylhomocystine and prevents synthesis of cystathionine [2]. It is characterized in childhood by low IQ [3], osteoporosis [4], skeletal disproportion, dislocation of the optic lens [5], cardiovascular risk and thromboembolic events [6]. Psychiatric disturbances [7,8] are present in up to 50% of patients [9,10]. HCU is rare, with a worldwide incidence of 1:65,000 to 1:900,000 [11], although it is predicted it could be as high as 1:6400 [12] and 1:15,500 [13] in some European countries.

In the absence of newborn screening programmes, diagnosis is commonly delayed. As a consequence, if patients are not detected early, the condition is associated with significant long-term morbidity and mortality [14–16]. A high proportion of individuals with c.833T>c (p.1278 T) (pyridoxine-responsive HCU) remain undiagnosed [13], and may have a thromboembolic episode in the third decade of life [1].

The aim of treatment is to reduce the concentration of homocyst(e)ine (Hcy) in the plasma and tissues. Two treatment interventions are used either singly or in combination: 1) low methionine or low natural protein diet with a methionine-free L-amino acid supplement [17] (with or without the addition of vitamins, minerals, carbohydrates and lipids) and/or 2) betaine, a medicine which promotes the recycling of homocysteine to methionine thereby decreasing plasma Hcy concentrations [18]. Both interventions are effective in lowering blood Hcy concentrations but both are associated with substantial patient adherence issues [8,16,19,20]. Medical and dietary treatment of HCU varies between inherited metabolic disorder (IMD) centres and there is limited knowledge about dietary practices. Although many agree that the aim of any treatment is to lower total Hcy (tHcy) close to normal reference range, there is no international consensus which defines optimal biochemical control and monitoring in this disorder.

The aim of this paper is to compare current dietary management practices of European metabolic centres and examine dietary treatment of patients with B_6 non-responsive HCU. Treatment outcome measures are not reported.

2. Materials and methods

2.1. Study design

A questionnaire (26 multiple choice and short answer questions) was sent to all European members of the Society for the Study of Inborn Errors of Metabolism Dietitians Group (SSIEM-DG) in 2011. This was to collect retrospective life-time dietary management data of B_6 non-responsive HCU patients in existing care from each IMD centre.

In this cross-sectional audit, data was collected on: treatment (use of diet only, betaine only, or combination of diet and betaine) for each patient categorized into age groups, description of diet therapy, including prescribed natural protein or methionine intake (for diet only or diet and betaine), mean protein equivalent intake (from dietary protein/methionine and methionine-free L-amino acid supplement), use of cystine supplementation including dose and method of administration, treatment aims and frequency of monitoring of biochemical parameters (tHcy, free homocystine [fHcy], methionine and cyst(e)ine [Cys], and use of other nutritional supplements. Clinical outcome data was not included in this audit.

Ethical approval was not required for this study as no specific identifiable patient data was obtained or used.

3. Results

Questionnaires were returned from 29 IMD centres providing data on 181 patients with HCU: UK (14 centres, 108 patients), Germany (5 centres, 39 patients), Netherlands (3 centres, 19 patients), Switzerland (2 centres, 5 patients), Portugal (2 centres, 4 patients) and Belgium, France and Norway (1 centre per country, each with 2 patients). Newborn screening (NBS) was uncommon (28% [n = 8] of centres).

3.1. Patient description

The ethnic origin of patients was: white European 86% (n = 155); Black African/Caribbean 3% (n = 6); Pakistani 3% (n = 6); Indian 3% (n = 6); Arabic 3% (n = 5) and Turkish 2% (n = 3).

3.2. Treatment

The most common choice of treatment was a combination of measured/unmeasured diet and betaine (61%, n = 110 of all patients); followed by betaine alone (34%, n = 62) and then diet alone (5%, n = 9; all from the UK) (Table 1, Fig. 1). There was a declining preference for prescribing diet with increasing patient age, whilst the preference for using betaine only, increased with age particularly >16 years (Fig. 1). Treatment choice was influenced by previous experience: problems with diet alone (38% of centres), good experience with diet alone (31%) and efficacious therapy with betaine alone without the need for diet (21%).

3.3. Treatment versus age of diagnosis (Table 2)

Only 19% (n = 25/131) of those with a known age of diagnosis were identified by NBS. All patients on 'diet only' treatment had been diagnosed by the age of 10 years (50%; n = 4/8 on NBS). Those on 'betaine only' were mainly (42%, n = 11/26) diagnosed after 10 years of age, 8% (n = 2/26) by NBS and in 36 patients the diagnostic age was unknown. Patients on 'diet and betaine' were mostly (84%; n = 81/97) diagnosed by the age of 10 years and 19% (n = 19/97) by NBS.

The age of diagnosis was unknown for just over one quarter of patients (28%; n = 50/181); all aged >16 years at the time of data collection and the majority (72%; n = 36) on a treatment of 'betaine only'.

3.4. Allocation of natural protein using methionine analysis

Approximately one half (52%, n = 15) of IMD centres prescribed a diet primarily using methionine analysis of foods. However, in practice