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Review

Adult classical homocystinuria requiring parenteral nutrition: Pitfalls and management

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SUMMARY

Background: Homocystinuria due to cystathionine beta synthase (CBS) deficiency presents with a wide clinical spectrum. Treatment by the enteral route aims at reducing homocysteine levels by using vitamin B6, possibly methionine-restricted diet, betaine and/or folate and vitamin B_{12} supplementation. Currently no nutritional guidelines exist regarding parenteral nutrition (PN) under acute conditions.

Methods: Exhaustive literature search was performed, in order to identify the relevant studies describing the pathogenesis and nutritional intervention of adult classical homocystinuria requiring PN. Description of an illustrative case of an adult female with CBS deficiency and intestinal perforation, who required total PN due to contraindication to enteral nutrition.

Results: Nutritional management of decompensated classical homocystinuria is complex and currently no recommendation exists regarding PN composition. Amino acid profile and monitoring of total homocysteine concentration are the main tools enabling a precise assessment of the severity of metabolic alterations. In case of contraindication to enteral nutrition, compounded PN will be required, as described in this paper, to ensure adequate low amounts of methionine and others essential amino acids and avoid potentially fatal toxic hypermethioninemia.

Conclusions: By reviewing the literature and reporting successful nutritional management of a decompensated CBS deficiency using tailored PN with limited methionine intake and n-3 PUFA addition, we would like to underscore the fact that standard PN solutions are not adapted for CBS deficient critical ill patients: new solutions are required. High methionine levels (>800 μmol/L) being potentially neurotoxic, there is an urgent need to improve our knowledge of acute nutritional therapy.

1. Introduction

Classical homocystinuria is an inherited metabolic disease caused by the deficiency of cystathionine β synthase (CBS) leading to an accumulation of homocysteine (Hcy), plasma methionine, and low-normal to reduced plasma cysteine (Fig. 1). Hcy being cytotoxic, it must be detoxified or removed from the body. Affected patients can show single or multiple organ involvement including vascular, respiratory, musculoskeletal, neurological and ocular symptoms [1]. Thromboembolism affecting any vessel is the major cause of morbidity and early death [2]. Fatal episodes of thromboembolic phenomena may occur following general anesthesia and/or surgery if not diagnosed before or if there is poor metabolic control [3–5]. In a historical cohort of 164 CBS deficient patients with 241 major surgical procedures 14 post-operative thromboembolic events were reported, including 4 fatal cases [3,6].

Recently, guidelines for the management of CBS deficiency were published including oral and/or enteral management [7]. Treatment aims at reducing Hcy levels by using vitamin B_6 and when necessary methionine-restricted diet, betaine and/or folate and vitamin B_{12} supplementation. While the pharmacological

Abbreviations: CBS, cystathionine β synthase; Hcy, homocysteine; tHcy, total homocysteine; hyper-Hcy, hyperhomocysteinemia; ICU, intensive care unit; IEM, inborn error of metabolism; EN, Enteral nutrition; PN, Parenteral nutrition; Met, methionine; NAC, N-acetylcysteine; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; BCAA, Branched chain amino-acids.

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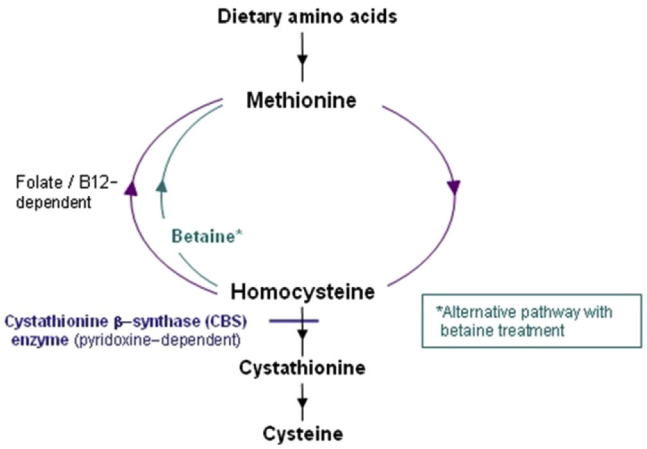

Fig. 1. A simplified pathway of methionine metabolism and homocysteine remethylation. Classic homocystinuria is caused by deficiency of cystathionine β-synthase (CBS), a pyridoxine (vitamin B_6)-dependent enzyme. Because homocysteine is at the branch point between transsulfuration and methionine remethylation in the methionine metabolic cycle, a block at CBS limits transsulfuration and results in both increased homocysteine and increased methionine, the latter caused by enhanced remethylation. Reproduction authorized by GeneReviews, University of Washington. Figure available at: https://www.ncbi.nlm.gov/books/NBK1524/

management is well known and described [1], there are currently no specific nutritional recommendations during critical illness when the digestive route is contraindicated.

We recently managed a young critically ill patient with homocystinuria and absolute contraindication to enteral feeding and were confronted to the absence of scientific information on how to manage this acute unusual situation. By reviewing the existing literature and sharing our experience, we hope to give the opportunity to intensive care physicians to have a pathway to follow in the planning and management of critically ill homocystinuric patients requiring complex parenteral nutrition (PN) until it will be integrated in future guidelines and/or consensus.

2. Methods

2.1. Literature review methodology

An exhaustive review of English literature was performed to identify all relevant articles describing the pathogenesis, nutritional intervention and outcome of classical homocystinuria requiring PN. To this purpose, we searched Pubmed, EMBASE™, CINHAL, Web of Science and Cochrane databases for relevant articles. Related search terms were used as follows: “classical homocystinuria”, “cystathionine-beta synthase deficiency”, “critical care”, “guidelines”, “parenteral nutrition”, “methionine”. Additional studies of interest were identified by hand searches of bibliographies. The search was last updated on July 4, 2017.

2.2. Illustrative case: patient description

A 22-year-old woman was admitted to the adult ICU of the Lausanne University Hospital on the 2nd day after a high velocity motor vehicle accident (MVA). She had a history of acute pulmonary embolism 3 month prior to admission that occurred in the context of the initiation of contraception. She was on oral anticoagulation with rivaroxaban. Hypercoagulability workup had revealed hyperhomocysteinemia (hyper-Hcy) of 350.2 μmol/L. The patient was suspected to have an inborn error of metabolism (IEM) and planned to be referred to an Expert Center. In the meantime, no specific treatment had been initiated. Upon hospital admission, torso injuries with a mesenteric disinsertion were diagnosed. On next day, she developed septic shock with moderate kidney and liver failure. After reversal of anticoagulation an exploratory laparotomy resulted in an intestinal resection for localized ischemia (intestinal extremities were closed and left in the abdomen). She was admitted to the ICU in shock under high dose norepinephrine. Fluid resuscitation and antibiotherapy were carried out according to guidelines. The shock resolved in 3 days: a 2nd look required a vacuum assisted closure (VAC) of the laparostomy. Renal and liver abnormalities resolved over 5 days. A 3rd look on day 5, enabled reanastomosis of the small intestine, and closure of the abdominal wall, but the surgeons denied enteral access for feeding. Despite reduction of sedation, the patient remained comatose (Glasgow Coma score 6). Brain magnetic resonance imaging (MRI) on day 9 showed small axonal lesions but no anomalies of the white matter, nor cerebral edema. She then progressively improved under Met restricted PN with n-3 polyunsaturated fatty acids (PUFAs), enabling extubation on day 12.

2.3. Laboratory methods

Free plasma amino acids were measured using the Biochrom 30 (Biochrom Ltd., Cambridge, UK) amino acid analyzer. The instrument has a specific program to separate the amino acids. After postcolumn derivatization with ninhydrin, the absorbance is monitored at 440 and 570 nm. Trace elements were determined by inductively coupled plasma system coupled to mass spectrometry (ICP-MS; 7700 Series; Agilent, Palo Alto). Cystathionine β synthase activity in fibroblasts, genomic amplification and direct sequencing of all the coding exons of CBS, including the flanking intronic regions were performed at the Division of Metabolism and Children's Research Center, University Children's Hospital Zurich, Pr Dr MR. Baumgartner.

2.4. Metabolic and nutritional management

Laboratory findings are reported in Table 1. Due to the extremely high tHcy (347 μmol/L) and methionine levels (952 μmol/L; range reference: 20–40 μmol/L) the attending metabolic physician (CT) was asked for opinion. Suspicion of CBS deficiency was raised and intravenous (IV) vitamin B_6 (40 mg bid), vitamin B_{12} (1 mg three times weekly), folinic acid (5 mg tid) were introduced on day 3.

Based on a body weight (BW) of 83 kg for 173 cm (Body mass index 27.7), the initial energy target was set at 1900 kcal/d (22 kcal/kg/d, 28 kcal/kg ideal BW) until an indirect calorimetry study showed an energy expenditure of 2740 kcal (32 kcal/kg, 40 kcal/kg ideal BW), and prescribed target was increased to 2200 kcal (Table 2).

Confronted with an absolute contraindication to enteral nutrition (EN) on 3rd ICU day (day 5 after MVA), PN was considered. Due to high methionine (Met) levels (952 μmol/L), a compounded solution was prescribed aiming at limiting Met intakes to below 250 mg/day. Aminosteril Hepa® was combined with Dipeptiven® (Fresenius Kabi, Stanz, Switzerland; Table 3) despite the initially high glutamine value which was attributed to the shock state, and because no other single IV amino acid was available. Glutaminemia was monitored, and reverted to within and below normal ranges, despite its daily administration of 15 and up to 27 g/day. Protein prescription was first limited to 0.45 g/kg for 6 days and increased to 0.9 g/kg ideal BW thereafter under supervision of nearly daily Met levels. Hence most of the delivery of energy was from carbohydrates (280–300 g/day) and lipids (90 g/day i.e. 1.1 g/kg as Omegaven®: 80% of lipids as omega-3 fatty acids, and 20% as long chain triglycerides): triglyceridemia remained within normal

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