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Nutrition management guideline for maple syrup urine disease: An evidence- and consensus-based approach

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ABSTRACT

In an effort to increase harmonization of care and enable outcome studies, the Genetic Metabolic Dietitians International (GMDI) and the Southeast Regional Newborn Screening and Genetics Collaborative (SERC) are partnering to develop nutrition management guidelines for inherited metabolic disorders (IMD) using a model combining both evidence- and consensus-based methodology. The first guideline to be completed is for maple syrup urine disease (MSUD). This report describes the methodology used in its development: formulation of five research questions; review, critical appraisal and abstraction of peer-reviewed studies and unpublished practice literature; and expert input through Delphi surveys and a nominal group process. This report includes the summary statements for each research question and the nutrition management recommendations they generated. Each recommendation is followed by a standardized rating based on the strength of the evidence and consensus used. The application of technology to build the infrastructure for this project allowed transparency during development of this guideline and will be a foundation for future guidelines. Online open access of the full, published guideline allows utilization by health care providers, researchers, and collaborators who advise, advocate and care for individuals with MSUD and their families. There will be future updates as warranted by developments in research and clinical practice.

1. Introduction

The Genetic Metabolic Dietitians International (GMDI) and Southeast Regional Newborn Screening and Genetics Collaborative (SERC) have undertaken a multi-year project to develop nutrition management guidelines for rare inherited metabolic disorders (IMD) for which there are limited peer-reviewed studies to provide evidence for various aspects of treatment. The goals of this project are to foster optimum nutrition management of affected individuals, reduce the uncertainty and variability in management, and direct future research. The first of these guidelines to be completed is for nutrition management of maple syrup urine disease (MSUD). While developing this first guideline, the previously published methodology [1] for the process was refined, included in the web-based portal and will be utilized for future guidelines.

MSUD (OMIM #24860) is an IMD caused by branched-chain α-ketoacid dehydrogenase (BCKD) deficiency resulting in the accumulation of the branched chain amino acids (BCAA), leucine (LEU), isoleucine (ILE), and valine (VAL) and their corresponding α-ketoacids (BCKA).

Exogenous (dietary) BCAA are major precursors for protein synthesis. Normally, they are also used as an alternative energy source when consumed in excess of anabolic needs or during endogenous muscle

Abbreviations: Allo-ILE, alloisoleucine; BCAA, branched-chain amino acids; BCKA, branched-chain α-ketoacids; BCKD, branched-chain α-ketoacid dehydrogenase; CoA, coenzyme A; DRI, dietary reference intake; GMDI, Genetic Metabolic Dietitians International; HRSA, health resources and health administration; ILE, isoleucine; IMD, inherited metabolic disorders; Kcal, kilocalories; LEU, leucine; MeSH, medical subject heading; MS/MS, tandem mass spectrometry; MSUD, maple syrup urine disease; MySQL, a structured query language; NAD, nicotinamide adenine dinucleotide; NCBI, National Center for Biotechnology Information; PICO, population, intervention, comparison, and outcomes; PRO, protein; SERC, Southeast Regional Newborn Screening and Genetics Collaborative-Health Resources and Service Administration (HRSA) Region 3; TPP, thiamine pyrophosphate; VAL, valine.

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protein catabolism. The initial step in LEU, VAL, and ILE catabolism is a reversible transamination step to form the BCKAs: α-ketoisocaproic acid, α-keto-3-methylvaleric acid and α-ketoisovaleric acid. The second step is an irreversible oxidative decarboxylation step, within the inner mitochondrial membrane, catalyzed by the BCKD complex. It is a multi-enzyme macromolecule with three catalytic components (E1, E2, E3). The E1 component is made up of two E1α and two E1β subunits forming a heterotetramer. The catalytic components require the cofactors thiamin pyrophosphate (TPP) and flavin adenine dinucleotide (FAD) as well as the prosthetic group lipomide and two regulatory enzymes (a kinase and a phosphatase) [2].

MSUD is an autosomal recessive disorder. The genes encoding the various catalytic subunits/components (E1α, E1β, E2, E3, kinase, and phosphatase) have been mapped to chromosome loci: 19q13.1–13.2; 6q14; 1p31; 7q31–32, 16p11.2 and 4q22.1, respectively. MSUD-causing human mutations in five of the six BCKD genes (with the exception of the kinase) have been documented [2,3]. In a total of 78 cell lines from MSUD subjects, the large majority had mutations in the E1 subunits [4,5]. A common mutation among the Old Order Mennonites is Y393N, a point mutation in the E1α subunit [3]. Individuals with MSUD are always homozygous or compound heterozygous for mutations in the same BCKD gene [6].

In the classical form of MSUD, with less than 3% residual enzyme activity, symptoms occur soon after birth. In the untreated neonate, the odor of maple syrup may be detected in the cerumen as early as 12–24 h, and in the urine by 48–72 h after birth. Elevated plasma concentrations of the BCAA including the unique BCAA alloisoleucine (allo-ILE), as well as a generalized disturbance of plasma amino acid concentration ratios are present by 12–24 h of age; elevated BCKA and generalized ketonuria, irritability, and poor feeding by 24–72 h; deepening encephalopathy manifesting as lethargy, intermittent apnea, opisthotonus, and stereotyped movements such as “fencing” and “bicycling” by 4–5 days; and coma and central respiratory failure may occur by 7–10 days. Other phenotypes with various degrees of partial enzyme activity include the intermediate, thiamin-responsive, and intermittent forms of MSUD that can lead to severe metabolic intoxication and encephalopathy with catabolic stress [6].

Newborn screening using tandem mass spectrometry (MS/MS) [7] has the potential for early detection allowing early initiation of treatment for MSUD. Although there is the possibility of false positives due to generalized aminoacidemia, or hydroxyprolinemia [8] and false negatives for milder variants of MSUD [9] rapid follow up of positive newborn screening reports should result in fewer infants demonstrating the severe clinical symptoms in the newborn period [10]. Mutation analysis and enzymatic testing, although not necessary for diagnosis, may help predict severity of the disorder or thiamin responsiveness [5].

The goals of medical nutrition therapy in MSUD are to rapidly reduce toxic metabolites by restricting dietary BCAA to amounts allowing individuals to achieve and maintain plasma BCAA amino acid concentrations within the targeted treatment ranges; reduce catabolism; promote anabolism; monitor nutritional status and alter intake to promote normal growth, development and health maintenance; evaluate thiamin responsiveness if the individual has residual BCKD activity; and supplement with thiamin if the individual is responsive. Heretofore, the treatment practices utilized to achieve these goals have varied. The process and resulting guideline described in this report are based on evaluation and summary of published and practice literature, consensus and expert opinion regarding nutrition management of MSUD.

2. Methods

The Nutrition Management Guideline for MSUD is an evidence- and consensus-based guideline created through a rigorous, transparent and systematic development process [1]. The process, created for this project, was adapted from the Academy of Nutrition and Dietetics [11] with the addition of specific techniques to draw on the expertise from clinical practice to provide information where published research is lacking [1].

2.1. Question formulation

The MSUD workgroup consisted of eight experienced metabolic dietitians who began the process by independently identifying over 40 practice areas where uncertainty and/or variation in practice existed. These were categorized and prioritized. Five topics were identified for evidence analysis and guideline development. Research questions for each topic were formulated in the PICO (population, intervention, comparison, and outcomes) format [12].

2.2. Search process

Because of the known scarcity of peer-reviewed scientific literature in nutrition management of IMDs, the search process included both published scientific studies and gray, or practice, literature.

For the peer-reviewed literature, medical subject heading (MeSH) terms were specific to each question, but inclusion and exclusion criteria were the same for all questions. Eligibility for research questions was limited to human studies and published in English from 1985 to summer 2011 (except for the research question related to thiamin that used earlier references from 1971), with nutrition data included. There were no study-design, age or setting restrictions. PubMed was the primary database used. Searches were conducted by a research librarian. The titles and abstracts of identified articles were scanned for relevance and matched with inclusion/exclusion criteria by the workgroup. Excluded articles were noted and qualifying articles were gathered for review and abstracting. Reference lists within the identified articles were examined for additional resources. These were added if they contributed pertinent information.

Practice (or gray) literature sources, which are not accessible through standard search systems, include abstracts and presentations from scientific and practice-based meetings, clinical protocols and guidelines, unpublished research, communication among experts (including list-serves), professional newsletters, and book chapters. The search for gray literature involved requests to individuals (e.g., practitioners and researchers) and organizations through their professional list serves, as well as online searches for materials related to nutrition and MSUD. Identified resources were screened and prioritized for inclusion based on relevance and substantive information not available in scientific literature, and currency.

2.3. Critical appraisal and abstraction

Each scientific article was critically reviewed by a trained analyst using a Quality Criteria Checklist, and the study design and methodology, findings, and author's conclusions were abstracted to Evidence Abstract Worksheets [11]. Quality criteria addressed subjects' and control groups' selection and retention, intervention clearly described and followed, other intervening variables tracked, outcomes defined, measures validated, and appropriate statistical analysis. Based on the number of criteria met, each article was assigned a quality rating of positive, neutral or negative.

Practice resources were reviewed by workgroup members using a specially developed quality criteria checklist for gray literature that included the following: clear purpose, relevance to intended users, systematic development process, and clear clinical recommendations, applicable to practice, and free of conflict of interest.

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