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Liver transplantation for treatment of severe S-adenosylhomocysteine hydrolase deficiency☆

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ABSTRACT

A child with severe S-adenosylhomocysteine hydrolase (AHCY) deficiency (*AHCY* c.428A > G, p.Tyr143Cys; c.982 T > G, p.Tyr328Asp) presented at 8 months of age with growth failure, microcephaly, global developmental delay, myopathy, hepatopathy, and factor VII deficiency. Plasma methionine, S-adenosylmethionine (AdoMet), and S-adenosylhomocysteine (AdoHcy) were markedly elevated and the molar concentration ratio of AdoMet:AdoHcy, believed to regulate a myriad of methyltransferase reactions, was 15% of the control mean. Dietary therapy failed to normalize biochemical markers or alter the AdoMet to AdoHcy molar concentration ratio. At 40 months of age, the proband received a liver segment from a healthy, unrelated living donor. Mean AdoHcy decreased 96% and the AdoMet:AdoHcy concentration ratio improved from 0.52 ± 0.19 to 1.48 ± 0.79 mol:mol (control 4.10 ± 2.11 mol:mol). Blood methionine and AdoMet were normal and stable during 6 months of follow-up on an unrestricted diet. Average calculated tissue methyltransferase activity increased from 43 ± 26% to 60 ± 22%, accompanied by signs of increased transmethylation in vivo. Factor VII activity increased from 12% to 100%. During 6 postoperative months, head growth accelerated 4-fold and the patient made promising gains in gross motor, language, and social skills.

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1. Introduction

S-adenosylhomocysteine hydrolase (AHCY), encoded by *AHCY* on chromosome 20, catalyzes the cleavage of S-adenosylhomocysteine (AdoHcy) to adenosine and homocysteine. It plays a pivotal role in the transsulfuration–transmethylation cycle that regulates tissue methionine supply and distributes methyl groups among scores of substrates (Fig. 1) [1–3]. One of three tissue-specific methionine adenosyltransferases converts methionine to S-adenosylmethionine (AdoMet), which is the principal methyl donor in mammalian systems and establishes a complex array of equilibria with AdoHcy via more than 100 mammalian methyltransferase enzymes (Fig. 1).

It is estimated that between 0.6 and 1.6% of all human genes encode AdoMet-dependent methyltransferases [4], which modify diverse substrates (DNA, mRNA, tRNA, rRNA, proteins, lipids) and contribute to key biosyntheses (e.g. heme, ubiquinone, catecholamines, melatonin) [5]. Quantitatively, the highest demand for methyl groups is shared by three enzymes: guanidinoacetate *N*-methyltransferase (GAMT), phosphatidylethanolamine methyltransferase (PEMT), and glycine *N*-methyltransferase (GNMT) catalyze the synthesis of creatine, phosphatidylcholine, and sarcosine, respectively (Fig. 1). Together,

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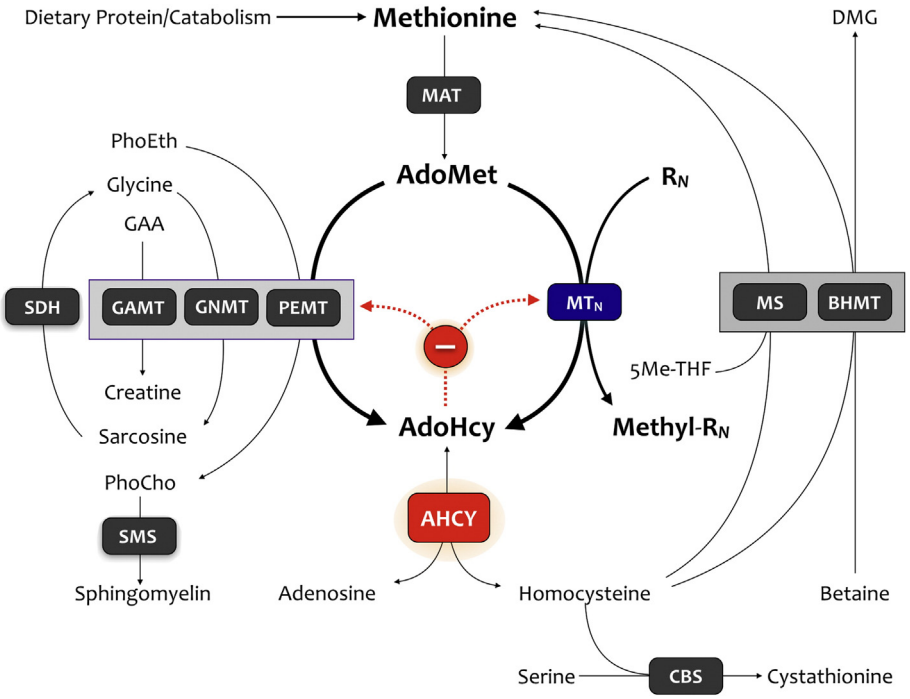

Fig. 1. Transsulfuration–transmethylation cycle and its major intermediates. Methionine is an essential amino acid derived from the diet and, to a more limited extent, endogenous protein catabolism. It can be recycled through the actions of 5-methylfolate (5Me-THF)- and vitamin B_{12}-dependent methionine synthase (MS) or betaine homocysteine methyltransferase (BHMT). Methionine is the source of S-adenosylmethionine (AdoMet), the principal methyl donor for transmethylation reactions in mammalian systems, ~85% of which occur in hepatocytes. Three enzymes—guanidinoacetate *N*-methyltransferase (GAMT), phosphatidylethanolamine methyltransferase (PEMT), and glycine *N*-methyltransferase (GNMT)—account for the majority of total transmethylation flux in humans. The glycine:sarcosine ratio in tissues is separately regulated by sarcosine dehydrogenase (SDH). Phosphatidylcholine is converted to sphingomyelin via the action of sphingomyelin synthase (SMS). More than 100 other methyltransferase enzymes (MT_N) distributed throughout human tissues mediate methyl transfer between AdoMet and diverse cellular substrates (R_N) to yield methyl-R_N and S-adenosylhomocysteine (AdoHcy). The latter is reversibly cleaved by AdoHcy hydrolase (AHCY) to yield adenosine and homocysteine, which is further metabolized by cystathionine beta-synthase (CBS) to produce cystathionine. AdoHcy is an allosteric inhibitor of most tissue transferases (indicated by red dotted lines).

these products account for the majority of total methyl flux in humans (5.7 to 14.0 mmol/m^2/day), but more than 30 other methylated compounds can be recovered from human urine [3,6].

A decade has passed since the first description of human AHCY deficiency [7]. Six additional case reports appeared in the literature between 2005 and 2012 [8–12]. Severe AHCY deficiency presents during infancy with some combination of growth failure, microcephaly, psychomotor delay, epilepsy, hypomyelination, myopathy, hepatopathy, factor VII deficiency, and marked elevations of blood methionine, AdoMet, and AdoHcy. A distinctive biochemical characteristic of AHCY deficiency is reversal of the normal AdoMet:AdoHcy molar concentration relationship, believed to exert control over numerous methyltransferase enzymes that may be regulated by feedback inhibition from AdoHcy (Fig. 1) [13,14]. Despite dietary interventions, developmental outcomes are poor [7–9].

Although AdoMet is synthesized in all mammalian cells, transsulfuration and transmethylation reactions are concentrated in the liver. On a whole body basis, hepatocytes synthesize 50% of AdoMet, mediate 85% of all transmethylation reactions [15,16], and have the highest AdoMet transmembrane gradient (~1400-fold) [17]. AHCY activity is similarly enriched in the liver, which has 4-fold higher *AHCY* mRNA expression than most other tissues and 10-fold higher gene expression than the brain (http://biogps.org/). Hepatic activity of AHCY is therefore a focal point of systemic AdoMet and AdoHcy homeostasis that can influence methylation status and physiological function of tissues throughout the body.

Here we describe a child with severe AHCY deficiency who received a liver segment from a healthy, unrelated living donor at 40 months of age. We observed significant and stable biochemical improvement, accelerated head growth, and developmental progress during 6 months of postoperative follow-up, suggesting a broader role for liver transplantation in treatment of human transsulfuration–transmethylation disorders.

2. Methods

2.1. Clinical and biochemical methods

The study was approved by the Institutional Review Board of Lancaster General Hospital and the proband's parents consented in writing to all procedures and practices. At 39 months of age, just prior to liver transplantation, the proband was evaluated for visual, linguistic, and motor skills using the Mullen Scales of Early Learning (AGS Edition) [18] and Peabody Developmental Motor Scales, 2nd Edition [19], Gross Motor Function Measure. Skill levels were represented as developmental quotients (DQ = developmental age/chronological age). Brain magnetic resonance imaging was obtained at 9, 18, 32, and 39 months of age.

Plasma AdoMet, AdoHcy, and related transsulfuration–transmethylation metabolites were measured by tandem mass spectrometry (Shimadzu Nexera LC System interfaced with a 5500 QTRAP® Sciex) as previously described [20] and quantified using stable isotopes. Total plasma homocysteine and 5-methyltetrahydrofolate (5-MeTHF) were determined by LC–ESI-MS/MS [21]. Choline and its metabolites in plasma were measured by liquid chromatography-stable isotope dilution-multiple reaction monitoring mass spectrometry as previously described [22]. Transsulfuration–transmethylation and choline analytes from the proband were compared to those from 36 healthy control subjects [22]. Plasma concentrations of fluoraldehyde-conjugated amino acids were measured by high-performance liquid chromatography (Agilent 1100 series) and results were compared to values from 51

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