



LAB #: B
 PATIENT:
 ID: -
 SEX: Female
 AGE: 49

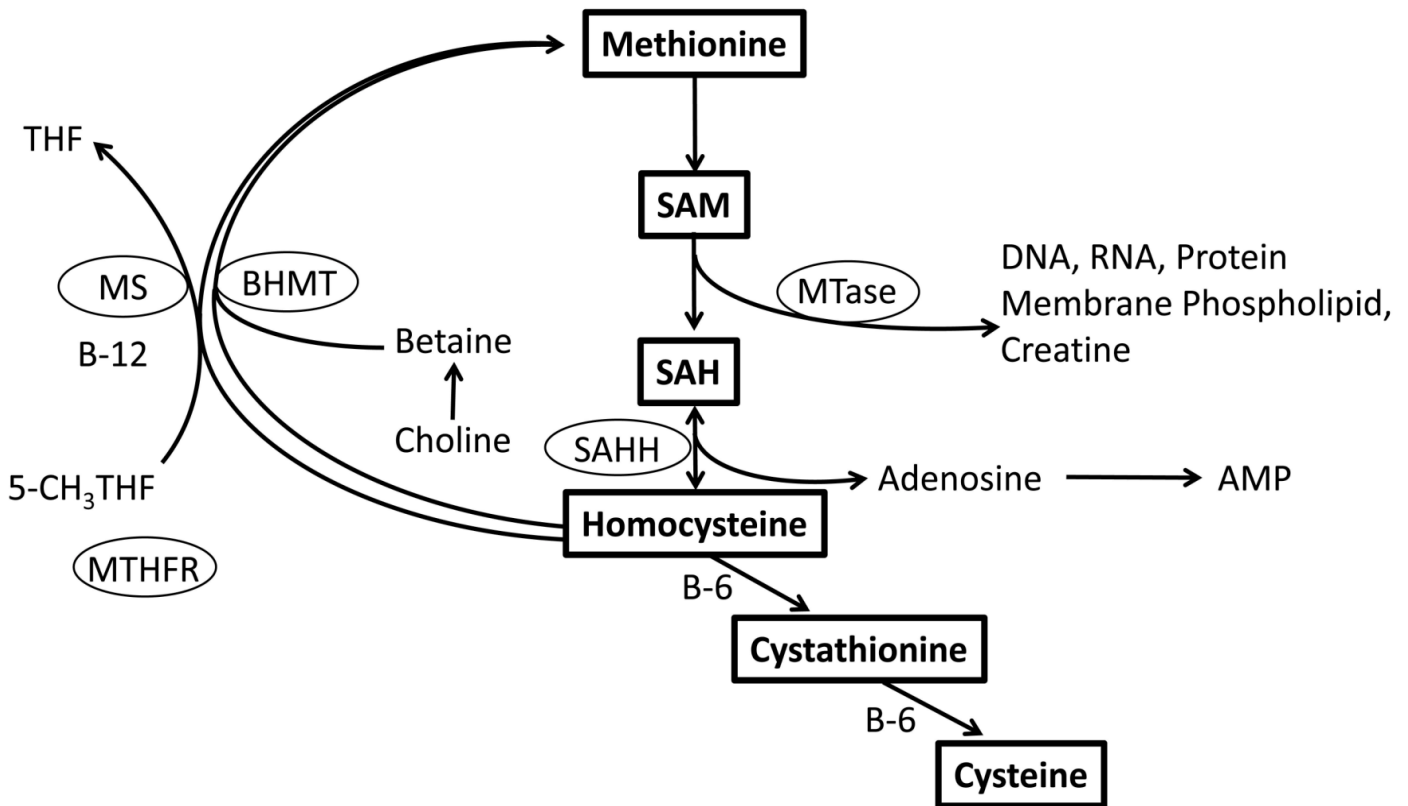
CLIENT #:
 DOCTOR:
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USA

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES							
	RESULT/UNIT	REFERENCE INTERVAL	PERCENTILE				
			2.5 th	16 th	50 th	84 th	97.5 th
Methionine	1.4 $\mu\text{mol/dL}$	1.6 - 3.6	[Bar chart showing result at 16th percentile]				
Cysteine	28 $\mu\text{mol/dL}$	20 - 38	[Bar chart showing result at 50th percentile]				
S-adenosylmethionine (SAM)	76 nmol/L	86 - 145	[Bar chart showing result at 16th percentile]				
S-adenosylhomocysteine (SAH)	18.6 nmol/L	10 - 22	[Bar chart showing result at 68th percentile]				
			68 th	95 th			
Homocysteine	4.7 $\mu\text{mol/L}$	< 11	[Bar chart showing result at 16th percentile]				
Cystathionine	0.01 $\mu\text{mol/dL}$	< 0.05	[Bar chart showing result at 2.5th percentile]				

METHYLATION INDEX				
	RESULT	REFERENCE INTERVAL	PERCENTILE	
			68 th	95 th
SAM : SAH	4.1	> 4	[Bar chart showing result at 68th percentile]	



SPECIMEN DATA			
Comments:			
Date Collected:	09/23/2013		
Date Received:	09/25/2013	<dl:	less than detection limit
Date Completed:	09/30/2013		
Method:	LCMS		v02.11

Introduction

This test assesses metabolism of the essential amino acid methionine (Met). Methionine is paramount in two metabolic processes; (1) transmethylation that is critical for the methylation of hundreds of important molecules such as DNA, RNA, proteins, neurotransmitters and membrane phosphatidylcholine, and (2) transsulfuration that leads to the biosynthesis of cysteine and hence glutathione, both of which have many important protective / detoxification functions. Aberrant Met metabolism can be caused by nutritional deficiencies, exposures to environmental toxicants and/or genetic polymorphisms and can have significant adverse health consequences. Identification of such abnormalities can guide appropriate nutritional intervention towards normalization of methionine metabolism and decreased risk and incidence of adverse health effects.

The amino acids and intermediary amino acid metabolites were measured by liquid chromatography - mass spectrometry. Reference values are age and sex specific. If patient values deviate from normal, comprehensive descriptive paragraphs will be presented as part of the test report.

Methionine low

Methionine (Met), an essential amino acid, is lower than expected. Methionine may be low due to imbalanced or inadequate protein intake or gastrointestinal dysfunction, including hypochlorhydria. Strict vegetarian diets commonly do not provide an adequate amount of Met. Methionine may also be low due to inadequate regeneration from homocysteine (methionine transmethylation cycle) that requires folate, B-12, betaine and normal activities of methionine synthase, methylenetetrahydrofolate reductase and betaine-homocysteine methyltransferase.

Methionine is incorporated into proteins and is a precursor of other important amino acids and metabolites. S-adenosylmethionine, derived directly from Met, provides methyl groups for hundreds of molecules such as serine, choline, creatine, melatonin, neurotransmitters, DNA, RNA, proteins, membrane phosphatidylcholine and other important molecules. Low Met, S-adenosylmethionine and elevated S-adenosylhomocysteine are associated with low cellular methylation capacity. Cysteine and taurine are also derived in part, from Met. Cysteine is the rate limiting amino acid in the cellular biosynthesis of glutathione, a predominant amino acid in metallothionein (intracellular metal binding protein), and is required for the production of Coenzyme A that is involved in fatty acid and carbohydrate (Krebs Citric Acid cycle) metabolism. Taurine is an important antioxidant, inhibitor of platelet aggregation, a component of bile, an inhibitory bioamine in the brain, and very importantly, an osmoregulator that facilitates the intracellular retention of magnesium and potassium (check red blood cell or whole blood magnesium levels).

Methionine deficiency can result in fatty liver, decreased cellular methylation and decreased capacity for endogenous detoxification of potentially toxic elements and chemicals. Symptoms that may be associated with insufficient Met include inflammation, oxidative stress, headaches, fatigue, biliary insufficiency (malabsorption of fat and fat soluble vitamins), hypercholesterolemia, occlusive arterial disease, myopia, osteoporosis and other skeletal disorders. Cheeses, fish, poultry, meats and some nuts (e.g. Brazil nuts, almonds and cashews) are good dietary sources of Met. Supplementation with Met should be accompanied by magnesium, B-6, folate, betaine and B-12.

References:

1. James SJ, Melnyk S, Fuchs G et al. Efficacy of methylcobalamin and folic acid treatment on glutathione redox status in children with autism. *Am J Clin Nutr* 2009;89:425-30.

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2. James SJ, Cutler P, Melnyk S et al. Metabolic biomarkers of oxidative stress and impaired Methylation capacity in children with autism. *Am J Clin Nutr* 2004;80:1611-7.
 3. Lu SC. Regulation of glutathione synthesis. *Mol Aspects Med* 2009;30:42-59.

S-adenosylmethionine low

S-adenosylmethionine (SAM), the first direct metabolite of normal methionine metabolism, is lower than expected. Up to half of daily methionine uptake is enzymatically converted in the liver to SAM by methionine-adenosyl transferase in the presence of ATP and magnesium. Therefore SAM may be low due to (1) low availability of methionine (check plasma methionine) (2) magnesium deficiency (check whole blood or red blood cell magnesium levels), (3) inhibition of methionine synthase activity, or (4) genetic or chemical inhibition of methionine adenosyltransferase activity. In the latter case, severe depletion of SAM can be associated with DNA hypomethylation and demyelination in the central nervous system. When dietary methionine and choline are insufficient, the folate-dependent pathway for regeneration of methionine from homocysteine is upregulated increasing the cellular requirement for folate. A potential consequence of the diversion of folate 1-carbon methyl groups towards regeneration of methionine (and SAM) may be functional depletion of folate methyl groups for DNA metabolism and integrity with potential for genetically significant consequences (e.g . genomic DNA hypomethylation). It is uncertain whether physiological decreases in SAM alone induced by nutritional deficiencies are causally related to cellular hypomethylation (*J Biol Chem* 2000;275:29318-23).

SAM is the principal biological methyl donor and participates in three important pathways in the liver; (1) polyamine synthesis (cell growth), (2) transmethylation, and (3) transsulfuration. Normally most of SAM is used in transmethylation reactions as a donor of its methyl group to a diverse group of hundreds of important molecules via the catalytic activity of methyl transferases. Molecules that require methylation for normal biological activity include, but are not limited to, DNA, RNA, proteins, choline, membrane phosphatidylcholine, creatine (liver), neurotransmitters and neurotransmitter receptors. Potential consequences of low SAM and compromised methylation include aberrant neurotransmitter metabolism, abnormal gene expression and silencing, immune dysregulation (autoimmunity), cancer, cardiovascular disease and vascular occlusion, congenital heart disease/birth defects, neurodegenerative disease, poor response to environmental toxins (e.g. endogenous detoxification of arsenic), and increased risk for Down Syndrome and perhaps autism spectrum disorder. While low SAM can be associated with under methylation, it has been suggested that the most sensitive indicator of poor methylation is the relative plasma concentrations of SAM to S-adenosylhomocysteine (methylation index). If SAM and methionine are low but the reported methylation index is normal, the condition may be remedied with appropriate intake/supplementation with methionine, folate, B-12, B-6, betaine and magnesium. Cheeses, fish, poultry, meats and some nuts (e.g. Brazil nuts, almonds and cashews) are good dietary sources of Met. Supplementation with Met should be accompanied by magnesium, B-6, folate, betaine and B-12.

References

1. James SJ, Melnyk S, Pogribna M et al. Elevation in S-adenosylhomocysteine and DNA hypomethylation: potential epigenetic mechanism for homocysteine-related pathology. *J Nutr* 2002;132:2361S-66S.
2. Yi P, Melnyk S, Pogribna M et al. Increase in plasma homocysteine associated with parallel increase in plasma S-adenosylhomocysteine and lymphocyte DNA hypomethylation. *JBC* 2000;275:29318-23.

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Patient:

Plasma Methylation

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3. James SJ, Melnyk S, Jernigan S et al. Abnormal transmethylation/transsulfuration metabolism and DNA hypomethylation among parents of children with autism. *J Autism Dev Disord* 2008;38:1966-75.
4. Lu SC. Regulation of glutathione synthesis. *Mol Aspects Med* 2009;30:42-59.