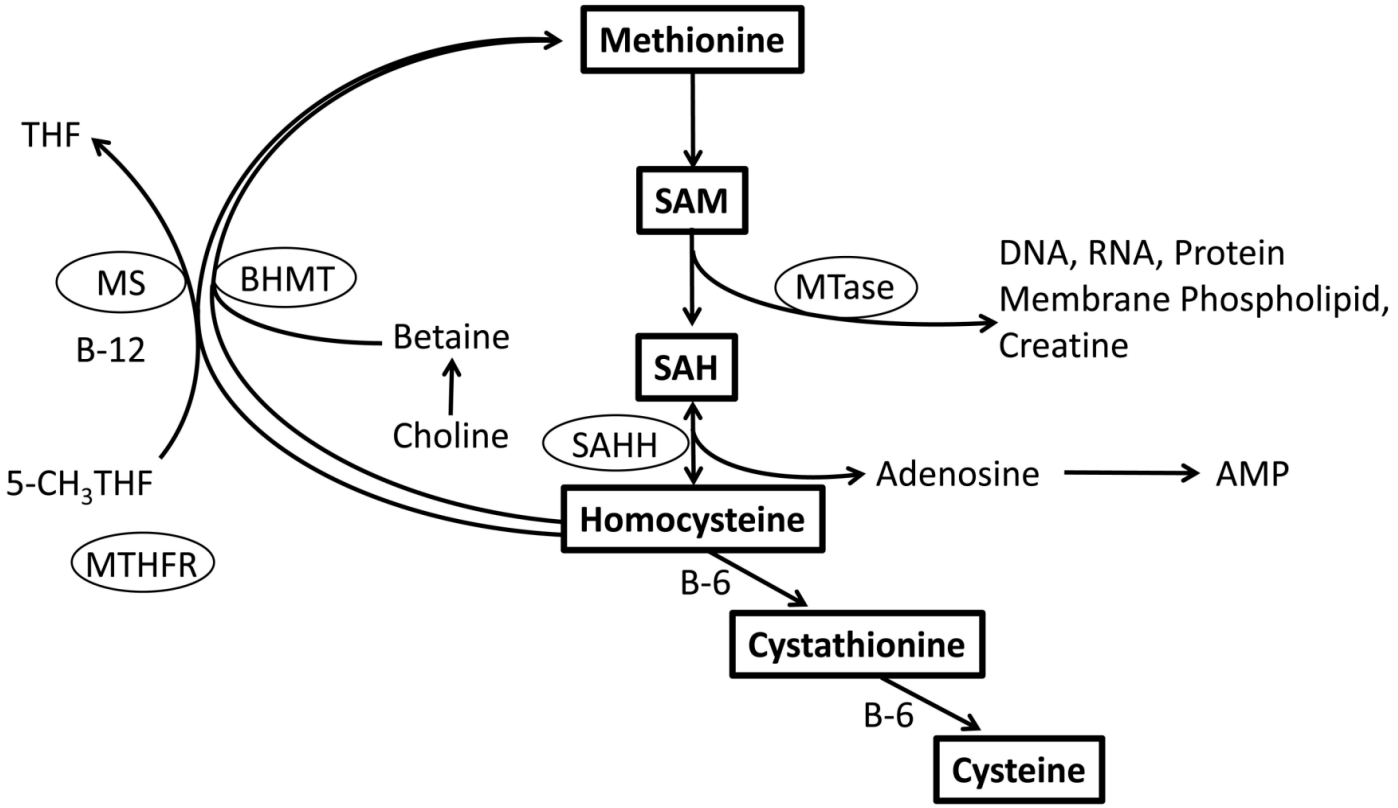
LAB #: Sample Report
PATIENT: Sample Patient
ID:
SEX: Female
DOB: 01/01/1985 AGE: 33

CLIENT #: 12345
DOCTOR: Sample Doctor
Doctors Data Inc
3755 Illinois Ave
St. Charles, IL 60174 U.S.A.

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES	RESULT/UNIT	REFERENCE INTERVAL	PERCENTILE (2.5th, 16th, 50th, 84th, 97.5th)
Methionine	1.9 µmol/dL	1.6 - 3.6	
Cysteine	25 µmol/dL	20 - 38	
S-adenosylmethionine (SAM)	62 nmol/L	86 - 145	
S-adenosylhomocysteine (SAH)	19.1 nmol/L	10 - 22	
Adenosine	19 nmol/L	20 - 80	
			68th, 95th
Homocysteine	5.4 µmol/L	< 11	
Cystathionine	0.01 µmol/dL	< 0.05	

METHYLATION INDEX	RESULT	REFERENCE INTERVAL	PERCENTILE (68th, 95th)
SAM : SAH	3.2	> 4	



SPECIMEN DATA

Comments:

Date Collected: **09/04/2018**
Date Received: **09/07/2018**
Date Completed: **09/07/2018**
Method: **LCMS**

<dl: **less than detection limit**

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.

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) transsulfurration. 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 suggeted that the most sensitive indicator of poor methylation is the relative plasma concentrations of SAM to S-adenysylhomocysteine (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-andenosylhomocysteine and lymphocyte DNA hypomethylation. JBC 2000;275:29318-23.

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.

Methylation Index Low

The methylation index, a sensitive indicator of cellular methylation capacity, is lower than expected. The methionine index represents the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH). A low value for the methylation index indicates limited capacity for methylation.

SAM is the principal biological methyl donor and normally most of SAM is used in transmethylation reactions to provide methyl groups to a diverse group of hundreds of important molecules including DNA, RNA, proteins, choline, membrane phosphatidylcholine, creatine (liver), neurotransmitters and neurotransmitter receptors. SAH is a potent inhibitor of methyltransferase enzymes (MTs), hence methylation. Potential consequences of compromised methylation include aberrant neurotransmitter metabolism, abnormal gene expression and silencing, cancer, cardiovascular disease and vascular occlusion, congenital heart disease/birth defects, neurodegenerative disease, autoimmune disease, poor response to environmental toxins (e.g. endogenous detoxification of arsenic), and increased risk for Down Syndrome and perhaps autism spectrum disorder. In a study of neurotypical (n=33) and autistic (n=20) children (ASD), plasma methionine, SAM and the methylation index (SAM to SAH ratio) were lower in the ASD group while SAH was significantly higher. An intervention trial was conducted with a subgroup of the ASD children (n=8) and it was demonstrated that supplementation with folinic acid, betaine and methyl-B-12 normalized the aforementioned indices of aberrant methionine metabolism and Methylation capacity.

SAM and SAH are substrates and products, respectively, of MTs and accumulation of SAH inhibits methyltransferase enzymes by product inhibition: SAH binds with high affinity to the active sites of MTs. Low SAM might be associated with inadequate methylation but, elevated levels of SAH, especially concomitant with low SAM has been shown to inhibit methylation of DNA in animal models. A low ratio of SAM to SAH, due to elevated SAH, was exhibited in patients with occlusive artery disease and elevated HCys. Similarly, elevated SAH in the presence of marginally decreased SAM was associated with hypomethylation of DNA and protein in patients with renal failure and elevated plasma levels of HCys.

In cells SAH accumulates when there is inefficient clearance of HCys. SAH is metabolized in a reversible manor by the enzyme SAH hydrolase (SAHH) to HCys and adenosine. The reversible activity of SAHH only proceeds in the direction of HCys if there is efficient removal of HCys and adenosine. Otherwise SAH is resynthesized from HCys by SAHH. Homocysteine is normally methylated to regenerate methionine in all

cells by the folate/B-12-dependent methionine synthase reaction and the betaine-homocysteine methyltransferase reaction (liver and kidneys). Alternatively homocysteine can be permanently removed from the methionine transmethylation cycle by conversion to cysteine via two irreversible B-6 dependent reactions (transsulfuration). Circumvention of accumulation of SAH and associated inhibition of methylation can be readily accomplished in most cases by appropriate supplementation with folate (or folinic acid), B-12 (or methyl B-12), B-6 (or P-5P) and betaine.

References

1. Yi P, Melnyk S, Pogribna M et al. Increase in plasma homocysteine associated with parallel increase in plasma S-andenosylhomocysteine and lymphocyte DNA hypomethylation. JBC 2000;275:29318-23.

2. James SJ, Cutler P, Melnyk S at al. Metabolic biomarkers of oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr 2004;80:1611-7.

3. 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.

4. Richardson B. DNA Methylation and autoimmune disease. Clin Immunol 2003;109:72-9.

5. Loeher F, Tschopl M, Angst C et al. Disturbed ratio of erythrocytes and plasma S-adenosylmethionine/S-adenosylhomocysteine in peripheral arterial occlusive disease. Atherosclerosis 2001;154:147-54.

6. Perna A, Castaldo P, DeSanto N et al. Plasma proteins containing damaged L-aspartyl residues are increased in uremia: implications for mechanisms. Kidney Int 2001;59:2299-2308.

Adenosine Low

The level of adenosine is lower than expected. Adenosine is released by S-adenosylhomocysteine hydrolase (AHCY) when S-adenosylhomocysteine (SAH) is hydrolyzed to homocysteine. Low activity variants or impaired activity of AHCY (nicotinamide) may result in high levels of SAH and low levels of adenosine. SAH levels may also increase if homocysteine levels are elevated, as high homocysteine levels may reverse the by-directional activity AHCY and use adenosine to synthesize SAH. Low levels of adenosine may reflect mitochondrial dysfunction and compromised ATP synthesis. Increased metabolic demand for AMP may decrease adenosine levels. Adenosine levels may decrease and AMP levels increase during intense physical activity, metabolic stress, or hypoxia.

Long-term excess alcohol or fructose ingestion may also decrease extracellular adenosine levels and cellular adenine nucleotides. Low levels of adenosine may possibly result from high activity or over-expression of the enzymes adenosine kinase (ADK), adenosine deaminase (ADA), AMP deaminases (AMPD) or adenylate (AK) isoforms. 5'-nucleotidases (zinc and magnesium) synthesize adenosine from ATP, adenosine diphosphate (ADP), or AMP.

Adenosine, the anti-inflammatory metabolite of adenosine triphosphate (ATP), acts to counter the pro-inflammatory signaling associated with its precursor ATP. Protective functions of adenosine include the regulation of oxygen use (via altered blood flow, respiration, tissue temperature, and cell metabolic rates), the induction of tolerance to low oxygen conditions, the regulation of angiogenesis and immune responses.

Low plasma adenosine has been associated with cardiovascular disease, inflammatory immune responses, and altered respiratory or neurological function. Adenosine serves as a neuromodulator in the central nervous system (CNS) and may help regulate the sleep-wake cycle. Low adenosine levels may promote neuron excitotoxicity. Adenosine promotes the insulin-mediated uptake of glucose by cells. Dysregulation of AMP signaling may contribute to diabetes, obesity and cardiomyopathy. Altered purinergic signaling due to altered ATP and adenosine levels has been associated with increased inflammation, insulin resistance, and vascular injury and may disrupt liver cell regeneration. Adenosine and ATP modulate the transcription of metallothionein genes; low levels of metallothionein may affect the safe intracellular availability of zinc, and detoxification of and toxic elements (in vitro). The vasodilator pentoxifylline appears to require adequate levels of adenosine for the compound's pharmacological effects

Consider:
-DNA Methylation Profile to evaluate SNPS in SAHH (AHCY)
-Red Blood Cell (RBC) Elements to evaluate intracellular magnesium and zinc status
-Mitochondrial supports such as CoQ10, á-lipoic acid, acetyl-L-carnitine, magnesium, selenium, zinc, resveratrol, vitamin C, thiamine
- Heavy exercise training may increase the activity of 5'-nucleotidases.