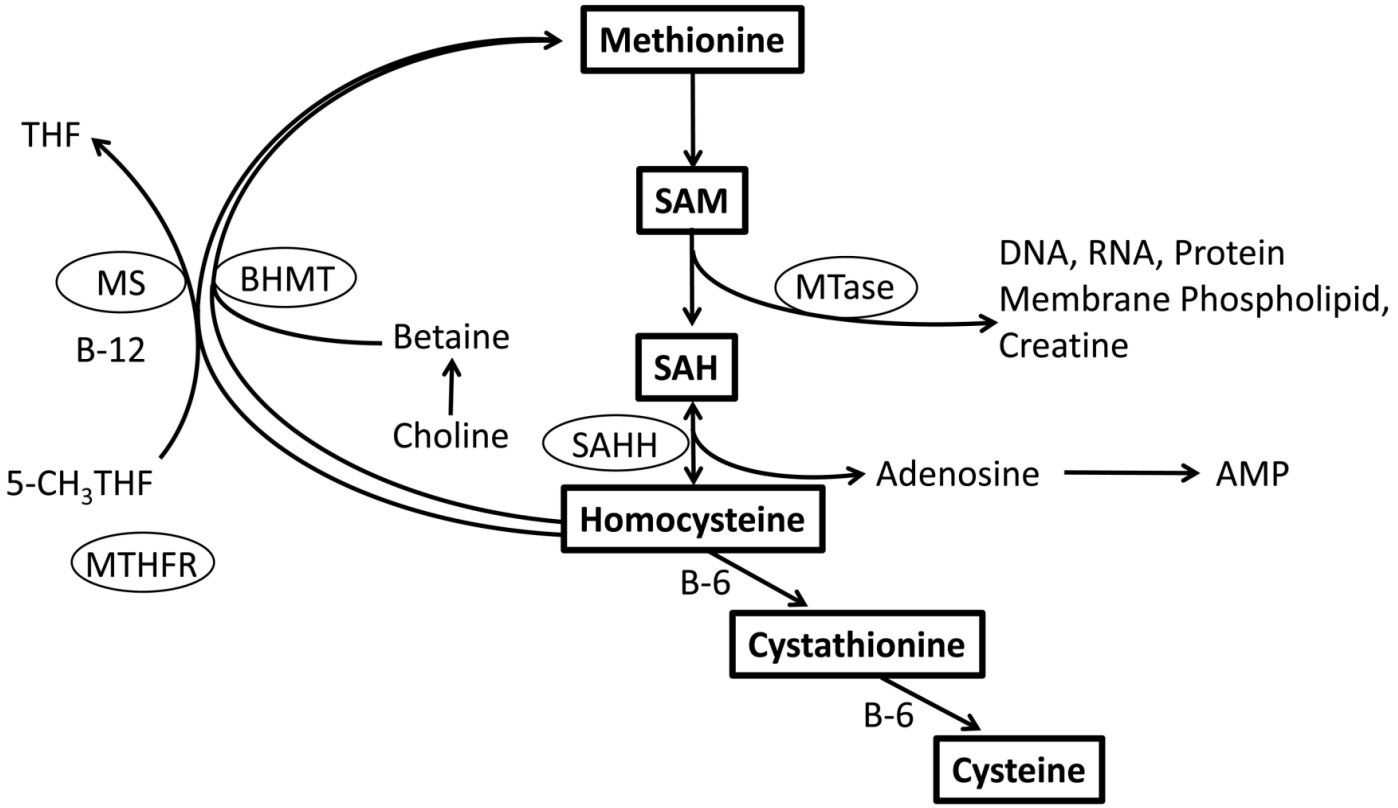
LAB #: Sample Report
PATIENT: Sample Patient
ID: P0000000000
SEX: Male
DOB: 01/01/1959
AGE: 58

CLIENT #: 12345
DOCTOR: Sample Doctor
Doctor's 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	**1.5 nmol/L**	1.6 - 3.6	
Cysteine	**18 nmol/L**	20 - 38	
S-adenosylmethionine (SAM)	**91 nmol/L**	86 - 145	
S-adenosylhomocysteine (SAH)	**20.4 nmol/L**	10 - 22	
Adenosine	**121 nmol/L**	20 - 80	
			68th, 95th
Homocysteine	**5.7 nmol/L**	< 11	
Cystathionine	**0.01 nmol/L**	< 0.05	

METHYLATION INDEX	RESULT	REFERENCE INTERVAL	PERCENTILE (68th, 95th)
SAM : SAH	**4.5**	> 4	



SPECIMEN DATA

Comments:

Date Collected: **07/16/2018**
Date Received: **07/18/2018**
Date Completed: **07/20/2018**
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.

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 of methionine synthase, methylenetetrahydroflate 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 methycobalamin and folinic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr 2009;89:425-30.

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. Lu SC. Regulation of glutathione synthesis. Mol Aspects Med 2009;30:42-59.

Cysteine low

Cysteine (Cys), a conditionally essential amino acid that is derived directly from dietary protein, breakdown of endogenous protein and indirectly from methionine (Met) via transsulfuration. Methionine is converted to homocysteine through a series of enzymatic reactions referred to as the methionine transmethylation pathway. Homocysteine can then be ”converted back to methionine via methylation reactions. Alternatively, in response to intracellular feedback mechanisms, homocysteine can be metabolized to cysteine via the transsulfuration pathway. Here, B-6 dependent cystathionine-beta synthase (CBS) condenses homocysteine with serine to form cystathionine then cystathionine is cleaved by B-6 dependent-cystathionase to release free cysteine. Cysteine can be low due to: (1) inadequate dietary intake of sulfur containing amino acids, (2) malabsorption, (3) B-6 insufficiency or limited ability to convert B-6 to active P-5-P, (4) Met insufficiency or impaired Met metabolism (insufficient amounts of folic acid, B-12, B-6, magnesium), (5) limited CBS activity, (6)oxidative stress and/or insufficient antioxidant status (vitamins E and C), (7) prolonged inflammation, (8) over-exposure to toxic metals and/or chemicals, (9) low activities of extracellular gamma-glutamyltranspeptidase/dipepdidase, (10), prolonged excessive use of DMSA, (11) cysteinurea . Additionally, recent research indicates that opiate-peptides formed from casein and gliadin can inhibit the binding and uptake of cysteine by epithelial cells in the gastrointestinal tract.

Cysteine is required for the formation of coenzyme A, proteins with cross-linked polypeptide chains (e.g. insulin), metallothionein, and enzymes with active sulfhydryl (SH-) groups (eg. glutathione peroxidase, Na/ K ATPase), and is the primary source of free sulfate. Cysteine is the rate limiting amino acid for the formation of intracellular glutathione, which is one of the most important antioxidants/detoxifying and regulatory molecules in the body.

Poor Cys status may be associated with chemical/environmental intolerances, increased retention of toxic metals and persistent organic pollutants, frequent inflammation, food intolerances, abnormal glucose metabolism, fatigue, myalgia, degeneration of ocular tissue, skeletal disorders, seizures, mental retardation, spasticity, brittle hair or premature thinning of hair, and weak or splitting fingernails. Supplementation with N-acetyl cysteine may be beneficial except in cystinuria (kidney stones), intestinal candidiasis or insulin-dependent diabetes. Undenatured whey protein, eggs and legumes are excellent dietary sources of Cys.

References

1. Lu SC. Regulation of glutathione synthesis. Mol Aspects Med 2009;30:42-59.
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.

Adenosine High

The level of adenosine is higher than expected. The normal conversion of S-adenosylhomocysteine (SAH) to homocysteine and adenosine by S-adenosylhomocysteine hydrolase (AHCY) only occurs if adenosine (and or homocysteine) levels are sufficiently low to drive reversible AHCY activity towards homocysteine. If adenosine is elevated, the process may reverse and condense homocysteine and adenosine together to form SAH, an oxidative stressor similar to homocysteine. Such has been reported in association with autism in which adenosine is often elevated, but homocysteine is low to normal. High levels of SAH inhibit methyltransferase activities and impair endogenous detoxification. Excess adenosine is generally the result of pathologic processes, although adenosine may be given in the treatment of a variety of cardiovascular medical conditions. Excess extracellular adenosine may also affect vascular tone,cardiovascular function, inflammatory status, renal function, immunity and central nervous system function.

Adenosine levels may be elevated in association with asthma or chronic obstructive pulmonary disease. Chronic excessive ingestion of ethanol or fructose may result in increased plasma adenosine. Low activity or loss of function inherited variations in the enzymes of the ATPase family may raise plasma levels of adenosine and ATP. Under conditions of stress or distress (hypoxia, ischemia,tissue trauma, UV radiation, toxicants) adenosine levels may rise rapidly. Medications that may raise adenosine levels include coformycin, cyclosporine A, pentostatin, diazepam, dipyridamole, metformin, tacrolimus, and theophylline. Caffeine intake sufficient to promote oxidative stress (5 mg/kg body weight) may block adenosine receptors and increase adenosine. Elevations of ATP and adenosine may be elevated with intermittent oxidative stress or a recent acute condition, such as a bacterial infection. Adenosine monphosphate has been approved by the FDA as a ôbitter blockerö food additive; its potential effect on plasma adenosine levels is currently unknown.

Adenosine may be elevated due to the inhibition or low activity of several enzymes. Adenosine kinase (ADK, magnesium-dependent)converts adenosine into adenosine monophosphate (AMP). ADK is considered the primary a clearance pathway under normal conditions. Individuals with rare, loss-of-function ADK mutations have elevated blood methionine, inhibition of transmethylase enzymes, liver pathology and encephalopathy. Adenosine deaminase (ADA, requires zinc) irreversibly deaminates adenosine into inosine; ADA has been reported to be low in a cohort of autistic children. Dipeptidyl peptidase IV (DPPIV) binds to the soluble extracellular ADA enzyme and may increase plasma adenosine. Adenylate kinase (AK) isoforms maintain energy homeostasis by interconverting ATP, ADP and AMP. AK mutations (AK1, AK2, or AK7 isoforms) may be associated with elevated plasma adenosine.