AMINO ACID DISORDERS

Methionine Adenosine Transferase (MAT) Deficiency

What is Methionine Adenosine Transferase (MAT) Deficiency?

Isolated persistent hypermethioninamia has been defined as abnormal elevation of plasma methionine that persists beyond infancy and is not caused by homocystinuria due to cystathionine ß-synthase deficiency, tyrosinemia type I or severe liver disease.[1] With rare exceptions, this abnormality has been found to be due to inactivating mutations in MAT1A, the gene that encodes the catalytically active subunit of the two isozyme forms of methionine adenosyltransferase.[2]

CLINICAL MANIFESTATIONS

The great majority of patients have no clinical abnormalities except for unpleasant, sulfurous breath odor but a few patients have shown neurologic abnormalities such as nystagmus, dysdiadochokinesis, increased tendon reflexes, mental retardation, dystonia and dysmetria associated with demyelination on MRI.[3] The complete lack of MAT I/III activity can represent a risk for development of brain demyelination, but some residual activity seems to be sufficient to maintain clinical well-being.[4]

PATHOPHYSIOLOGY

The pathogenesis of this disease is not clearly elucidated and it might result from different factors: extraordinarily high plasma methionine levels can directly contribute to nuerological abnormalities, the lack of synthesis of S-adenosylmethionone (AdoMet)-dependent methylated products can cause demyelination and hyperhomocysteinemia might bring about an elevated risk of vascular and thrombotic dieases.[4]

Inheritance: autosomal recessive[4, 5]

CONFIRMATORY TESTING

Plasma amino acids and urine organic acids (methylmalonic acid). Further confirmatory testing may be required after referral to a metabolic specialist.

Overview of Disease Management

Treatment is generally not indicated but in patients with evidence of demyelination, administration of S- adenosylmethionine corrects deficiency of this compound.[3,5] Initiation of management should be done in consultation with an attending physician/ metabolic specialist.

Prognosis

Abnormal elevations of plasma homocysteine have been reported among more severely affected MAT I/III deficient patients and might possibly increase the long-term risk for strokes.[4]

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

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WHAT TO DO

If unwell and cannot tolerate oral intake:

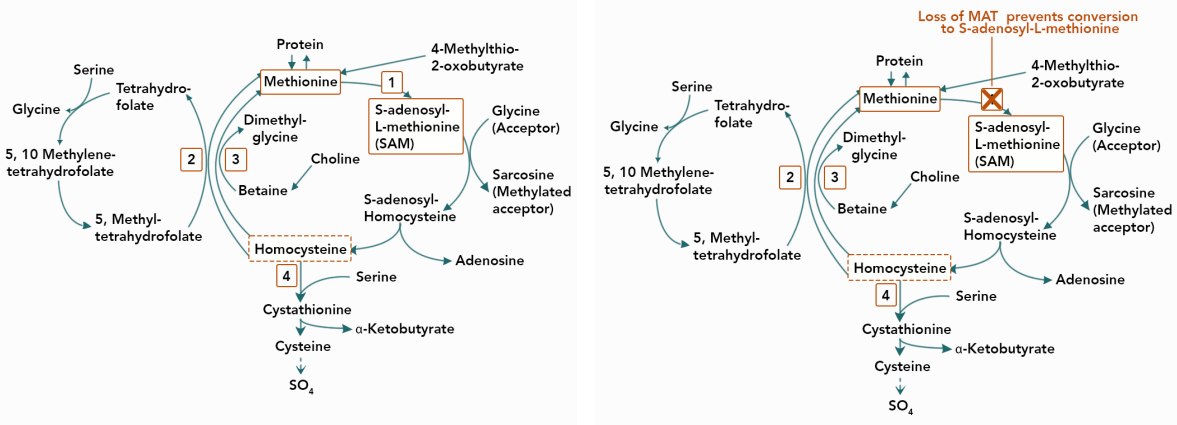
- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Collect plasma amino acid sample. May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Collect plasma amino acid sample. May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours).

**Children should not be protein restricted for longer than necessary (24-48 hours)*
**Inform the metabolic doctor on call for further guidance regarding on-going management*
**If the patient is well, coordinate with a metabolic specialist regarding further management.*

Normal break-down of protein vs MAT Deficiency patient's break-down of protein



[1] *Mudd SH, Chamberlin ME, Chou JY. Isolated persistent hypermethioninemia: genetic, metabolic and clinical aspects. As cited in Kim SZ, Santamaria E, Jeong TE et al. Methionine adenosyltransferase I/III deficiency: two Korean compound heterozygous siblings with a novel muta on. J Inherit Metab Dis 2002;25:661-671.*
[2] *Kim SZ, Santamaria E, Jeong TE et al. Methionine adenosyltransferase I/III deficiency: two Korean compound heterozygous siblings with a novel mutation. J Inherit Metab Dis 2002;25:661-671.*
[3] *Fowler B. Chapter 16: Disorders of Transsulfura on in Sarafoglou K, Hoffman GF and Roth KS (eds). Pediatric Endocrinology and Inborn Errors of Metabolism. New York:McGraw Hill, 2009 pp 185-194.*
[4] *Martins E, Marcao A, Bandeira A et al. Methionine Adenosyltransferase I/III Deficiency in Portugal: High Frequency of a Dominantly Inherited Form in a Small Area of Douro High Lands. JIMD Reports 2011.*
[5] *Adria G, Fowler B, Sebas o G. Chapter 21: Disorders of Sulfur Amino Acid Metabolism in Fernandes J, Saudubray JM, van den Berghe G, Walter JH (eds). Inborn Metbaolic Disease Diagnosis and Treatment 4th ed. Germany:Springer Medizin Verlag, 2006 pp 278-279*