AMINO ACID DISORDERS

Homocystinuria (Hcy)

What is Homocystinuria (Hcy)?

Homocystinuria (Hcy) is caused by cystathionine ß-synthase deficiency is an inborn error of the transsulfation pathway which causes an increase in levels of homocysteine and methionine in blood.[1]

CLINICAL MANIFESTATIONS

Patients affected with homocystinuria may present with (1) ectopia lentis which is found in 85% of patients[2]; (2) skeletal abnormalities are prominent especially genu valgus and patients are often described to have a "marfanoid habitus"; (3) mental retardation is common but not invariable and; (4) thromboembolism.[2,3]

PATHOPHYSIOLOGY

Increased homocysteine levels is found to inhibit linking of collagen and elastic tissue, which predisposes zonule generation of the eye predisposing patients to myopia and lens dislocation.[4] Skeletal abnormalities are thought to result from damage to fibrillin in patients with cytathionine ß-synthase and due to a reduction in collagen crosslinking[5] while the mechanism that contributes to the atherogenic propensity of hyperhomocystinemia are related to endothelial dysfunction and injury, which leads to platelet aggregation and thrombus formation.[6] Finally, chemical abnormalities and the repeated thromboemolic strokes may contribute to the mental retardation.[4,6]

Inheritance: Autosomal recessive[7]

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

The aim of treatment is to reduce the plasma total homocysteine through the following approaches: (1) large doses of pyridoxine (50-100mg/day) have been effective in reducing biochemical abnormalities in patients with cystathionine-ß-synthase deficiency where about half respond partially (2) folic acid (10mg/day) may be given along with betaine (100mg/ kg/day) that lowers homocysteine levels by remethylation dietary modification by giving a low-methionine/high-cystine diet. [2] Additional treatment may include Vitamin C (100mg/day) and hydroxocobalamin (1mg/day) starting at 5 yrs of age. Initiation of management should be done in consultation with an attending physician/metabolic specialist.

Prognosis

Early diagnosis and treatment can prevent thromboembolic events and reduce the complications brought about by increased levels of homocysteine.[2]

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:

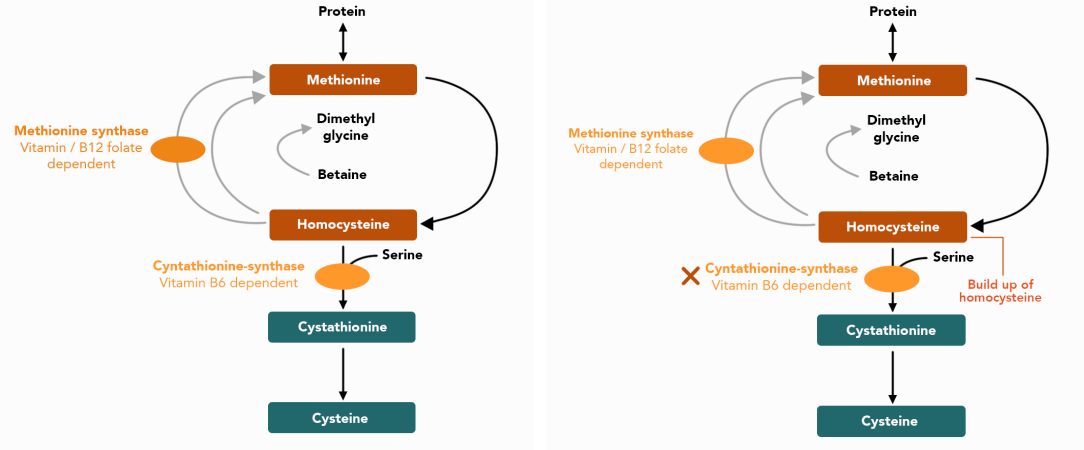
- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Collect samples for plasma amino acids. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if the patient requires it.
- Start D12.5% 0.3NaCl at full maintenance. Assess the patient and clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start betaine, folic acid and vitamin B6.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with HCY formula or protein free formula at maintenance rate
- Insert IV access. Collect samples for plasma amino acids. May request for investigations (i.e. CBC, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Start betaine, folic acid and vitamin B6.
- Monitor input and output strictly (q6 hours)

*Children should not be protein restricted for longer than necessary (24-28 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 breakdown of protein vs Homocystinuria patient's breakdown of protein



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