Classical Homocystinuria: Disease State and Treatment Options

Summary

- Classical homocystinuria (HCU) is caused by deficiency of CBS enzyme, and is the most common inherited disorder of Hcy metabolism[1]
- HCU presents deficiencies in 4 body systems, causing skeletal deformities, connective tissue defects, thromboembolism, and cognitive impairment[2]
- Current SOC includes dietary restrictions, treatment with betaine, pyridoxine (vitamin B6), and folates; however, not all patients are responsive to available therapies, resulting in a high unmet need for new treatments[2,3]

Classical HCU

HCU Disease State and Underlying Causes

Classical HCU is an inherited genetic defect of methionine metabolism, causing insufficient activity of the pyridoxine-dependent enzyme CBS and interruption in the synthesis pathway of Cys from methionine.[1,3,4] This disruption results in accumulation of Hcy in blood, tissues, and urine.[4,5] HCU presents as 1 of 2 variants, pyridoxine-responsive or pyridoxine-nonresponsive; pyridoxine-responsive is typically milder than the nonresponsive variant.[6]

Methionine, Hcy, Cys, and taurine are essential sulfur-containing amino acids; of this group, methionine and Cys are incorporated into proteins.[3] Hcy is produced from dietary methionine via the transsulfuration pathway, which then utilizes CBS to convert Hcy to cystathionine for the synthesis of Cys. An alternative pathway for Hcy metabolism is via the remethylation of methionine by the cobalamin (vitamin B12)-dependent enzyme methionine synthase, using the folate derivative 5-MTHF as a methyl donor.[1] With insufficient CBS activity, Hcy can reach toxic levels, along with elevated levels of methionine, resulting in multisystem pathologies.[3]

Normal tHcy is defined as <15 μM; specifically, 5-15 μM is considered healthy. Increases in tHcy are further characterized as[7]:

- Moderate: 16-30 μM
- Intermediate: 31-100 μM
- Severe: >100 μM

Until recently, prevalence of HCU was estimated at ~1 in 200,000-335,000 cases worldwide, and ~1 in 100,000-200,000 in the US. HCU is poorly detected in newborns, resulting in underestimation of the disease and a significant number of false negatives. Assessment of research databases in the US determined that prevalence is possibly ≥10 times previous estimates, with ~1 in 10,000 people in the US population.[5]

Clinical Presentation

HCU is a multisystemic disease and presents as symptoms in the ocular, skeletal, vascular, and central nervous systems. Expression of clinical signs is variable and can range from mild to severe, with patients manifesting anywhere from 1 to all system impairments.[5,6] Ocular symptoms include ectopia lentis, which is present in ~50% of cases, with disruption of zonular fasers and high-grade myopia. Skeletal abnormalities and connective tissue defects are prominent and include *genu valgum*, dolichostenomelia, moreover pectus excavatum or carinatum. Osteoporosis associated with scoliosis is one of the most characteristic symptoms of HCU.[3,4]

Psychiatric disorders and cognitive deficits associated with HCU have been reported in >50% of patients, including behavior disorders, depression, OCD, anger and aggression, anxiety, suicidal ideation, and personality disorders. Patients may manifest one or more psychopathologies throughout the course of the disease. Intellectual disability and cognitive delay may also present in patients with HCU, with neurocognitive test scores in the low range or below the normative population.[8]

Life expectancy may be limited in patients with HCU; thromboembolism, peripheral arterial disease, myocardial infarction, and stroke are frequent causes of mortality. Thromboembolism of small and large arteries and veins is the most prominent cause of morbidity and mortality and is due to damage resulting from elevated amino acid levels. About 30% of patients suffer a thromboembolic event by age 20, and ~50% experience this event by age 30.[4]

Diagnosis

Classical HCU is characterized by high or high/normal methionine level, plasma tHcy usually >100 µM, normal B12 and folate levels, and normal MMA. Testing for HCU may be prompted by clinical indications, including neurological symptoms, learning deficits, thromboembolism, and lens dislocation. Testing should include vitamin B12 and folate measurements and assessment of kidney function. If high plasma tHcy is detected, causes other than HCU should be ruled out, including drugs and toxins. Additional measures should include quantitative Cys and methionine, and plasma and urine MMA. If test results show high or high/normal methionine, tHcy >100 µM, normal folate and B12, and normal MMA, there is a likely diagnosis of classical HCU. Diagnosis should be confirmed with mutation analysis, assessment of lens dislocation, and evaluation of pyridoxine responsiveness.[1]

Treatment of HCU

Current Treatments

Available therapies for HCU are limited and frequently inefficient. This is in part due to low patient adherence to strict dietary restrictions. Treatment is primarily focused on decreasing and preventing accumulation of Hcy and maintaining plasma tHcy concentration at <100 µM in adults and <50 µM in children. With this reduction in tHcy, there is decreased risk of thromboembolic events, lens subluxation is halted, and there is normal progression of bone growth in children. Central to this goal is a low methionine/low protein diet, combined with a methionine-free supplement to provide other necessary amino acids. Treatment also often includes supplementation with folate and vitamin B12. For patients who cannot reach or maintain acceptable levels of Hcy, betaine is a possible treatment option. Patients with pyridoxine-responsive HCU may benefit from vitamin B6 supplements. Concomitant complications of HCU should also be addressed, such as surgery for ocular abnormalities.[1,3,6] A review of current therapies is presented in **Table 1**.[3]

Table 1. Current Therapies for HCU

Therapy	Description	Type	Stage	Mechanism of action
Current therapies				
Met-restriction combined with Met-free amino acid formula	Low protein diet and Met-free amino acid formula to supply the missing amino acids	Diet	In clinical use	Reduces build-up of Hcy by limiting the consumption of its precursor Met. Most patients often find it hard to adhere to the diet.
Pyridoxine	Vitamin B_6	Diet supplement	In clinical use	CBS catalytic co-factor. Increases enzymatic activity of certain CBS mutants. Most HCU patients are either non-responsive or partially responsive.
Betaine	Trimethylglycine	Diet supplement	In clinical use	Promotes Hcy re-methylation to Met via liver-dependent BHMT. Results in build-up of Met. Decreased efficacy over time.

Future Therapies

Given the insufficiencies of available HCU therapies, there is a high unmet need for new treatment options. ERT and gene therapy are under development as novel approaches to treating HCU.[3] Additional therapies under investigation are liver-directed treatments, including liver tissue engineering, implantation of normal CBS enzyme activity, cells for liver regeneration, and liver transplants.[4]

HCU in Pediatric Patients

Prevalence of HCU is underestimated, partly due to ineffective newborn screening and frequent false negative results. Children appear normal at birth and symptoms typically do not appear before age 2 years, with the exception of psychomotor delay. If undiagnosed and untreated, multisystem disease progression and development of symptoms continues.[4]

To improve upon early detection of HCU, PSI-MS has been introduced. This method provides enhanced sensitivity in quantitative detection of biomolecules and metabolites.[4,9] With earlier diagnosis and initiation of treatment, HCU-related complications of ocular, skeletal, vascular, and central nervous symptoms may be prevented or lessened, including bone growth and normal intellectual ability. However, even with early intervention, learning difficulties that have already developed cannot be reversed by treatment.[1,4]

Abbreviations

5-MTHF, 5-methyltetrahydrofolate; BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine-β-synthase; cDNA, copy DNA; CGL, cystathionine gamma-lyase; Cys, cysteine; ERT, enzyme replacement therapy; HCU, homocystinuria; Hcy, homocysteine; Met, methionine; MMA, methylmalonic acid; OCD, obsessive-compulsive disorder; PEG, polyethylene glycol; PSI-MS, paper spray ionization mass spectrometry; rAAV, recombinant adeno-associated viral vector; RBC, red blood cell; SOC, standard of care; tHcy, total homocysteine; US, United States; WT, wild type.

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