Classical homocystinuria

Key facts

- Classical homocystinuria (HCU) is an autosomal recessive disorder caused by a deficiency in cystathionine β-synthase (CBS) that results in a defect in the catabolic pathway of the amino acid methionine.
- CBS is a pyridoxine (vitamin-B6) dependent enzyme that is responsible for the conversion of homocysteine to cystathionine. Deficiency therefore leads to the accumulation of homocysteine.
- The age of onset and disease severity varies markedly between patients.
- Two phenotypic variants exist; pyridoxine-responsive and pyridoxine-unresponsive.
- The prevalence of homocystinuria varies widely depending on ethnicity. The highest incidences have been reported in Qatar (1 in 1,800) and Ireland (1 in 65,000).
- Other causes of raised homocysteine include inborn errors of homocysteine remethylation, vitamin deficiencies (especially B12), renal insufficiency and medication.

Clinical features

- The severity of symptoms in HCU patients can vary markedly: from completely asymptomatic, to a severe multi-system disease.
- Pyridoxine-responsive patients generally have a milder phenotype and a later onset than those who are pyridoxine-unresponsive.
- The organs/systems that may be involved in classical HCU include:
  - Eye: lens dislocation (85% cases), and/or progressive myopia.
  - Skeletal system: marfanoid habitus, osteoporosis, pectus excavatum.
  - CNS: developmental delay/intellectual disability, psychiatric problems.
  - Vascular system: thromboembolism.
- Childhood presentation more commonly involves lens dislocation and developmental delay. Onset in adulthood is typically associated with thromboembolism.
- Thromboembolism is the major cause of morbidity and early death for those affected by the condition.

Diagnosis

- Frontline biochemical testing for the diagnosis of classical HCU includes the measurement of total homocysteine accompanied by plasma amino acid analysis, typically performed by specialist metabolic laboratories.
- Diagnosis is characterised biochemically by markedly raised concentrations of plasma total homocysteine and methionine (as determined by plasma amino acid analysis).
- HCU may also be diagnosed by tandem mass-spectrometry analysis of methionine in dried blood spots as part of newborn screening programmes, for example the NHS newborn blood spot screening (NBS).
- Pyridoxine (vitamin B6) challenge is often performed following diagnosis, prior to the initiation of treatment.

Genetic basis and genetic testing

- Classical HCU is an autosomal recessive condition, caused by variants in the *CBS* gene. Heterozygotes (carriers) are asymptomatic and do not develop homocystinuria.
- Families with an affected child should be referred for genetic counselling; this is particularly important in families where consanguineous marriage is customary, as there may be implications for the wider family.
- Prenatal or preimplantation genetic diagnosis requires the pathogenic variant in both parents to be identified.

Clinical management

- Management of HCU aims to correct biochemical abnormalities, primarily to control the elevated plasma total homocysteine concentrations.
- Pyridoxine therapy is used in patients shown to be responsive, and may also be included in the treatment of those with evidence of non-responsiveness.
- Dietary treatment involves a methionine-restricted diet. This is typically managed by a specialist metabolic dietician, and monitored on the basis of plasma total homocysteine and methionine.
- Folate and vitamin B12 supplementation may be used to aid the conversion of homocysteine to methionine. Betaine therapy may also be instituted in patients with poor adherence to dietary treatment.

Direction to further reading and guidelines

- British Inherited Metabolic Disease Group: HCU clinical management guidelines
- British Inherited Metabolic Disease Group: HCU dietetic management pathway
- Newborn blood spot screening programme: supporting publications
- Expanded newborn screening HCU fact file

This information is intended for educational use and was current in November 2019. For clinical management, it is recommended that local guidelines and protocols are used.

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