Homocystinuria is a rare inherited metabolic disorder characterised by an increased blood and urine concentration of homocysteine - a sulfur-containing amino acid. Classical homocystinuria is due to a deficiency in cystathionine beta synthase (CBS). Affected individuals appear normal at birth but develop serious complications in childhood. Diagnosis and treatment started sufficiently early in life can effectively prevent or reduce the severity of these complications.[1]

Apart from CBS deficiency, there are six other distinct types of homocystinuria:

- 5,10-methylenetetrahydrofolate reductase deficiency.
- Deficiency of cobalamin in coenzyme synthesis - consists of five subtypes (cblC, -D, -E, -F and -G).

All the other forms of homocystinuria result from enzyme abnormalities involved in the conversion of homocysteine to methionine. This is catalysed by homocysteine:methylenetetrahydrofolate methyltransferase (also called methionine synthase) and its two cofactors - methylenetetrahydrofolate and methylcobalamin (methyl-vitamin B12). These cases are severe and rarely reported; thus, experience with treatments and other data are limited.[2]

The rest of this article discusses classical homocystinuria caused by CBS deficiency.

Pathophysiology

It results from reduced activity of the enzyme CBS which is involved in the conversion of methionine to cysteine. The enzyme is mapped to gene locus 21q22.[3] Homocysteine and methionine accumulate in tissues and interfere with the cross-linking of collagen fibres.

Epidemiology

The G307 S mutation is the most common cause of homocystinuria in patients of Celtic origin. Guthrie testing has shown the incidence to be 1 in 344,000 worldwide but it is much higher in Ireland (1 in 65,000). All cases are inherited as autosomal recessive. 50% are responsive to pyridoxine (vitamin B6) and tend to have milder disease.[3]

Clinical findings

- Raised plasma homocysteine that results in homocystinuria and raised plasma methionine levels.[4]
- 80% of homozygous patients will develop ocular abnormalities and half of these will have general learning disability.
- Abnormalities typically develop by the age of 3-4.

Heterozygous carriers (1 in 70 of the general population) have hyperhomocystinaemia - raised plasma homocysteine levels with no homocystinuria. Their risk of premature cardiovascular disease is increased.

Presentation

- Skeletal features: Marfanoid habitus with normal to tall stature (occasionally failure to thrive in infancy), fine, brittle hair, hypopigmentation, high arched palate, crowded teeth, arachnodactyly, limited joint mobility, pectus excavatum/carinatum, kyphoscoliosis.
- Eyes: dislocation of the lens usually downward and medially (ectopia lentis), myopia, glaucoma.
- CNS: general learning disability (average IQ = 80; 30% have normal IQ), seizures, cerebrovascular events, psychiatric disorders.[5]

Differential diagnosis

Marfan's syndrome is the main differential diagnosis to consider.[6]
## Marfan's syndrome
- Autosomal dominant
- Aortic incompetence
- Upwards lens dislocation
- Normal mentality
- Scoliosis
- Flat feet
- Herniae

## Homocystinuria
- Autosomal recessive
- Heart rarely affected
- Downwards lens dislocation
- General learning disability
- Recurrent thromboses
- Osteoporosis

The following conditions also elevate urinary cysteine levels:

- Elderly
- Postmenopausal
- Renal failure
- Hypothyroidism
- Leukaemia
- Psoriasis
- Drugs - eg, methotrexate, isoniazid

### Investigations
- The cyanide-nitroprusside test is an easy way to detect increased excretion of sulfhydryl-containing compounds in the urine.
- Urine amino acids - elevated homocysteine and methionine levels.
- Plasma levels of free methionine and homocysteine (methionine is raised in CBS deficiency and low or normal in those with other causes of homocystinuria).
- Ophthalmology tests to detect myopia and dislocated lens.
- Diagnosis depends on measurement of CBS activity in tissues - eg, liver biopsy, skin biopsy.
- Imaging: X-rays; dual-energy X-ray absorptiometry (DEXA) bone scans to detect osteoporosis.

### Complications
- Thromboembolism.
- Coronary artery disease - eg, myocardial infarction.
- Mitrval valve prolapse.
- Osteoporosis - in two thirds of patients by age 15.
- Fatty infiltration of liver.
- Pancreatitis.

### Management
- Effective treatment requires early diagnosis and initiation of therapy.
- Pyridoxine is the drug of choice. Patients may be divided into pyridoxine-sensitive and pyridoxine-insensitive:
  - Pyridoxine-sensitive: pyridoxine, folic acid, and vitamin B12 are used in combination to reduce the homocysteine levels.
  - Pyridoxine-insensitive: low-methionine diet is started at diagnosis; given along with betaine supplementation, it may help reduce homocysteine levels.

- Methionine restriction has been shown to prevent general learning disability and reduce the rate of lens dislocation and seizure activity.
- Avoid folate deficiency.
- Consider primary prevention of cardiovascular disease - eg, aspirin, statin.
- Referral to specialists as indicated by the clinical picture - eg, ophthalmologist, psychiatrist.

Prognosis

Early diagnosis and prophylactic medical and dietary care are essential and can halt or even reverse some of the complications[7].

Further reading & references

3. Homocystinuria; Online Mendelian Inheritance in Man (OMIM)
7. Picker JD, Levy HL; Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency

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