Phenylketonuria

Key facts

- Phenylkentonuria (PKU) is an autosomal recessive condition that prevents the body from metabolising the amino acid phenylalanine to tyrosine, due to a deficiency in the enzyme phenylalanine hydroxylase.
- Classic PKU results from complete enzyme deficiency, and therefore causes the most severe phenotype. This presents clinically within the first few months of life, when phenylalanine accumulates to toxic levels.
- The incidence of classic PKU is 1 in 10,000 in European populations. Prevalence is higher in Turkey (1 in 4,000), but is much lower in African American populations, with an incidence of 1 in 50,000.

Clinical features

- Patients often have fair complexions due to tyrosine deficiency.
- If not diagnosed in the neonatal period, classic PKU presents within the first few months of life with failure to thrive, eczema, vomiting and a musty odour. If it remains untreated, patients develop microcephaly, seizures and developmental and behavioural disorders.
- There are mild to moderate phenotypes of PKU in which patients have a varying degree of enzyme activity. These patients can tolerate low levels of phenylalanine in their diet (~500mg/day) but if these levels are exceeded, patients can develop cognitive dysfunction, as well as behavioural and developmental disorders in later childhood.
- The mechanisms by which elevated phenylalanine levels cause neurological dysfunction are still unknown.

Diagnosis

- Biochemical testing for the diagnosis of PKU is based on elevated levels of blood phenylalanine.
- Blood phenylalanine concentration in newborns is usually between 30 and 60 µmol/L. Elevated blood phenylalanine levels are classified as 120 µmol. In classic PKU, concentrations of phenylalanine may be very high (>1200 µmol/L).
- PKU can also be diagnosed using tandem mass spectrometry, as part of the NHS newborn blood spot screening programme in England. This method is used to detect high concentrations of phenylalanine and low concentrations of tyrosine.

Genetic basis and genetic testing

- Genetic testing can be used to confirm the diagnosis by detecting the pathogenic *PAH* variants, which can also be used for carrier detection.
- Non-*PAH* variants can cause hyperphenylalaninaemia due to tetrahydrobiopterin (BH4) deficiency. BH4 is an essential co-factor for PAH. Disorders of BH4 metabolism account for 2% of patients with elevated phenylalanine. Most BH4 metabolism disorders are inherited in an autosomal recessive pattern. Clinically, these present in a very similar way to PKU.
- 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

- Treatment should be initiated as soon as possible. In newborns, treatment usually begins before the child reaches one week of age.
- The mainstay of treatment is a low phenylalanine diet. This requires the use of foods with phenylalanine-free protein substitutes (amino acid mixtures). This is required lifelong, however poor palatability of the foods can negatively impact on patient adherence.
- Breastfeeding is encouraged for infants with PKU, as the levels of phenylalanine are lower in breast milk than formula milk. This should be alternated with phenylalanine-free formula, supervised by a specialist dietician.
- Target maintenance levels for blood phenylalanine are <6mg/dl for newborns and <10mg/dl for older children and adults.
- Blood concentrations of phenylalanine should be measured at regular intervals. The minimum frequency for routine monitoring is age dependent: 0-1 year, weekly; 1-12 years, fortnightly; >12 years, monthly. Increased frequency may be indicated following treatment changes, on clinical grounds or when querying adherence issues.
- When women affected with PKU reach child-bearing age, it is essential for them to be counselled about risks to their offspring. Adhering strictly to a low phenylalanine diet can prevent microcephaly and developmental delay occurring in the next generation.

Direction to further reading and guidelines

- Newborn blood spot screening programme: supporting publications
- Orphanet: phenylketonuria
- Uptodate: overview of phenylketonuria

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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