Screening brief

Phenylketonuria

Definition

- An autosomal recessive disorder, resulting in phenylalanine hydroxylase deficiency, raised blood levels of phenylalanine with normal or low tyrosine, and excess phenylketone and phenylamine production.[1] Over 400 genetic mutations have been identified. Most sufferers are compound heterozygotes.[2] Severity of the phenylketonuria (PKU) is related to blood phenylalanine level with a range 240–>3000 μmol/l (normal range 35–120 μmol/l)

Natural history

- Untreated, biochemically severe PKU (phenylalanine >1200 μmol/l) carries an 85% risk of mental handicap often with epilepsy and microcephaly.[1] Phenylalanine levels 600–1200 μmol/l (10% of cases) carry a less well quantified risk. A further 10% have phenylalanine levels 240–600 μmol/l. The threshold for impairment is poorly defined.[1 3]

Birth prevalence

- Estimates of prevalence vary. In the UK 1:10 000 newborns have phenylalanine levels persistently above 240 μmol/l and 1:14 000 above 1200 μmol/l.[4] European estimates vary from 1:4000 in Ireland and Iceland to 1:40 000 in Finland; 1:20 000 in the USA

Screening procedure

- Neonatal heel prick samples are collected on absorbent paper (Guthrie cards) or in capillary tubes, mostly at home at days 3–5, or days 6–14 in the UK.[4 5] In the absence of community services, collection is at the maternity unit. Samples taken within 24 hours are tested, but a repeat is recommended[6]
- Samples are tested by bacterial inhibition assay, fluorimetry, chromatography, enzyme assay, or tandem mass spectrometry
- Phenylalanine concentration used to define positives varies (120–240 μmol/l) with age at testing.[1 4–6] Typically, tyrosine is measured in the same blood sample to identify 0.2–0.3% of infants with secondary hyperphenylalaninaemia due to prematurity, intravenous feeding, sepsis, liver disease, tyrosinaemia, or galactosaemia[7]
- In 1–2% the hydroxylase cofactor, tetrahydrobiopterin, rather than the hydroxylase itself, is deficient. This should be tested for in all infants with raised phenylalanine as it can be treated successfully.[1 4]

Screening performance

- Detection rate and predictive value depend on laboratory technique, limits used for recall, and day of collection.[6] Detection rate with a 240 μmol/l limit at 6–14 days of age for detection of PKU disorder causing handicap is 99.7%[4]
- Initial false positive rate is around 0.2%[7 8]
- With these figures the odds of being affected given a positive result (OAPR) in the initial test in the UK would be 1:20 derived from (birth prevalence) × (detection rate/false positive rate) or (1:10 000) × (99.7%/0.2%), or (1:10 000) × 500 = 1:20. However, after additional testing on the same sample the OAPR is >10:1

Treatment

- A phenylalanine restricted diet dramatically improves outcome and its continuation in adult life is generally recommended, but the diet is demanding and associated with side effects (nutrient deficiency, social restriction, emotional disturbance)[1 3]
- Treatment is routinely offered for infants with phenylalanine ⩾600 μmol/l. Practice varies in infants with lower values[1 3]
- If a couple have an affected child antenatal diagnosis by DNA methods can be offered in subsequent pregnancies

Maternal PKU

- Infants of mothers with severe PKU untreated in pregnancy have a 90% risk of damage in utero (microcephaly, low birth weight, dysmorphic features, other congenital anomalies, and mental handicap).[1 9] Preconceptional treatment reduces these risks, though IQ may still be lowered[10 11]

Cost effectiveness of screening

- Screening is well established in most economically developed countries, and despite the rarity of the disorder is considered to be worthwhile
- The cost of screening is generally judged to be less than the cost of care in the absence of treatment and prevention[7]

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