SPECIAL REPORT

Recommendations on the dietary management of phenylketonuria

A working group convened by the Medical Research Council (MRC) has recently reviewed our current knowledge on phenylketonuria due to phenylalanine hydroxylase deficiency. Intellectual status in early treated subjects is not as good as was thought just a few years ago. The subtle but global intellectual impairments that have been documented are, to a very substantial degree, determined in the preschool years, long before there is any question of stopping or relaxing treatment. The impairments are also much more closely linked with the quality of phenylalanine control than previously recognised. In addition, there appear to be two factors associated with this phenomenon. General ability is closely associated with phenylalanine control in the preschool years and to a lesser extent the preadolescent years. In apparent correlation with executive tasks depend on current phenylalanine control.

Further link between neurological status and phenylalanine control is now emerging. In animals phenylalanine excess, even of moderate degree, leads to a dose related increase in myelin turnover. In human subjects with phenylketonuria undergoing magnetic resonance imaging (MRI) myelin structure has been shown to be abnormal in a proportion of older children and adolescents with phenylalanine concentrations greater than 400–500 μmol/l. The greatest changes are seen in subjects with the highest phenylalanine concentrations. Overt neurological deterioration has been described in a few subjects who have shown even more marked changes on MRI.

Maternal phenylketonuria is another important problem as the advantages of screening in one generation could be lost in the next unless preventative treatment can be implemented in a high proportion of affected women. Again there is good evidence of a close association between the size of the fetal affected and the quality of phenylalanine control, especially in the early weeks of gestation.

There is now need to appraise existing treatment protocols for phenylketonuria in the light of this new information bearing in mind the particular approach to treatment currently used in the UK. The need to promote a policy of continuing dietary treatment into adult life; advise women with phenylketonuria to return to a strict diet before conceiving; the importance of specialist services for the long term management of phenylketonuria; and the role of local services has already been stressed. The MRC working group has also produced the following set of guidelines on dietary management.

**Recommendations**

The guidelines given below cannot easily be achieved without certain changes in the way in which the diet is managed, in the composition of some of the products being used, and in the services available. For example, some of the methods currently used for measurement of blood phenylalanine concentrations will need to be improved and the frequency of monitoring will need to be increased. The system of 50 mg phenylalanine food exchanges will need to be refined and revised to encompass a much wider range of natural foods now allowed freely (for example many vegetables). Also manufacturers will need to consider the phenylalanine and amino acid contents of some of their special foods. The management of phenylketonuria is going to be even more taxing for the patients and their families than in the past.

1. Screening needs to be conducted so that diagnosis and treatment can begin with the minimum of delay, certainly by 20 days of age. Diagnostic investigation should include an assessment of protein intake, quantitative measurement of plasma amino acids, and exclusion of defective biotin metabolism.

2. All infants whose blood phenylalanine concentrations exceed 600 μmol/l, in the presence of a normal or low plasma tyrosine and an otherwise normal plasma amino acid profile while receiving a normal protein intake (2–3 g/kg/day), should start a low phenylalanine diet immediately. Infants whose blood phenylalanine concentrations remain persistently between 400 and 600 μmol/l for more than a few days should also start treatment.

3. The diet should contain a protein substitute which is phenylalanine free (or at least very low in phenylalanine) and otherwise nutritionally and compositionally complete with a composition sufficient to provide 100–120 mg/kg/day of tyrosine and a total amino acid intake of at least 3 g/kg/day in children under 2 years of age. In children over 2 years the intake of amino acids should be maintained at a level of 2 g/kg/day. The protein substitute should be spread as evenly as possible through the 24 hours.

4. If plasma phenylalanine concentrations exceed 900 μmol/l at diagnosis natural milks should be excluded for a short period to ensure a
Recommendations on the dietary management of phenylketonuria

427

made to continue treatment aiming at blood phenylalanine concentrations no higher than 700 μmol/l. Patients should know that, even at this phenylalanine concentration, there is evidence that performance on specific decision making tasks may improve if phenylalanine concentrations are reduced. However, given the major practical difficulties of treatment, especially in subjects with severe forms of phenylalanine hydroxylase deficiency, adolescents and young adults will have to make their own choices about their phenylalanine intake having been appraised of the risks of high phenylalanine concentrations.

(12) Adults and adolescents with phenylketonuria require continued delivery of services in an appropriate setting. Services must include facilities for frequent biochemical monitoring and dietetic advice (by post and telephone) and specialist medical adult services for both outpatient follow up and inpatient care. Adult physicians with a special interest in metabolic disease need to be linked to existing regional services.

(13) Female subjects require counselling with respect to the need to return to very strict dietary control before conception. It is important that family doctors, obstetricians, and family planning counsellors are aware of the importance of establishing dietary control before conception and are also aware of the scale of intervention required. Specialist dietetic and biochemical facilities with appropriate medical support are certainly required to implement effective treatment, and in patients who have not been taught a strict diet as an adult may well need a period of inpatient supervision.

(14) Those who conceive while phenylalanine concentrations are 900 μmol/l or above, should be offered termination of pregnancy because of the high risk of malformations. Even below this concentration hyperphenylalaninaemia poses some risk to brain growth and intellectual development so that the offer of detailed fetal ultrasound assessment and possible termination should extend to patients with phenylalanine concentrations of 700 μmol/l or above.

(15) Phenylalanine concentrations in pregnancy need to be at least as strictly (and probably more restrictively) controlled as in infancy. Due to the positive amino acid gradient across the placenta the fetus is exposed to even higher phenylalanine concentrations than the mother. Biochemical monitoring should be undertaken twice a week, both in the period before conception and during pregnancy, aiming at values of 60–250 μmol/l. Effective contraception should be continued until control has been achieved. Pregnancies require careful monitoring, using ultrasound to assess fetal growth and anatomy so that any fetal abnormalities can be identified as early as possible.

Conclusions

Services for children and adults with phenylketonuria need to be updated and expanded to take account of our new perceptions of this disorder. Specialist services will be best delivered by a unit for inherited metabolic disease.
