

SPECIAL REPORT

Recommendations on the dietary management of phenylketonuria

Report of Medical Research Council Working Party on Phenylketonuria*

A working group convened by the Medical Research Council (MRC) has recently reviewed our current knowledge on phenylketonuria due to phenylalanine hydroxylase deficiency.¹ 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 and there appear to be two components to this association. General ability is closely associated with phenylalanine control in the preschool years and to a lesser extent the preadolescent years. In addition performance on executive tasks depend on current phenylalanine control.

A further link between neurological status and phenylalanine control it 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 $\mu\text{mol/l}$. 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 affects 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 conception; the importance of specialist services for the long term management of phenylketonuria; and the role of local services has already been stressed.¹ 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 bipterin metabolism.

(2) All infants whose blood phenylalanine concentrations exceed 600 $\mu\text{mol/l}$, 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 $\mu\text{mol/l}$ 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 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 $\mu\text{mol/l}$ at diagnosis natural milks should be excluded for a short period to ensure a

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rapid fall of blood phenylalanine concentrations to below 600 $\mu\text{mol/l}$ (concentrations are likely to fall at a rate of 300–600 $\mu\text{mol/l/day}$) with daily monitoring of blood phenylalanine concentrations in order to judge individual requirements (usually between 60 and 110 mg/kg/day in the neonate) and to avoid phenylalanine deficiency.

(5) Families should be counselled with respect to genetic variability, prognosis, facilities for prenatal diagnosis, risks of pregnancy in girls, and the details of dietary management. Advice needs to be given by someone with a good knowledge of the disorder and the families need early access to the specialist services required for long term care.

(6) Blood phenylalanine concentrations taken at a standard time (ideally early morning when concentrations are likely to be at a peak) should be monitored at least weekly once intake has stabilised, aiming to keep phenylalanine concentrations between 120–360 $\mu\text{mol/l}$ (instead of the 180–600 $\mu\text{mol/l}$ widely used previously). Monitoring requires a postal service for phenylalanine analysis, more accurate laboratory micromethods (such as fluorimetry or high pressure liquid chromatography) than are currently used in many centres and frequent contact between the family and those responsible for the child's care. Biochemical monitoring should continue on a weekly basis up to at least 4 years of age. After 4 years and up to 10 years the frequency of monitoring can be reduced to fortnightly and, thereafter, monthly.

(7) Phenylalanine intake should be adjusted according to blood phenylalanine concentrations, taking care to monitor phenylalanine concentrations and intake (mg per day and per kg) serially so that this can be appropriately and promptly adjusted when blood phenylalanine concentrations rise or fall outside the therapeutic range.

(8) A standard protocol is needed for management of intercurrent illness to ensure the best possible intake of fluid, energy, and protein substitute. A high energy, low phenylalanine regimen should be implemented during such episodes. Phenylalanine intake should be re-established according to appetite, requirement, and blood phenylalanine concentrations.

(9) Overall nutrient intake, body growth, feeding pattern, and general health needs review every two to three months in infancy, three to four months up to school age, and every six months thereafter. In subjects with mild phenylketonuria treatment should only be withdrawn (protein substitute stopped) if their intake of natural protein reaches optimum requirements for age while blood phenylalanine concentrations remain below 400 $\mu\text{mol/l}$. Low protein diets and protein load tests are not recommended.

(10) Strategies aimed at getting children to be responsible for their own diet and blood tests by school age need to be much more actively promoted than in the past.

(11) The aim should be to maintain strict phenylalanine control as long as possible. An upper limit of 480 $\mu\text{mol/l}$ rather than 360 $\mu\text{mol/l}$ may be acceptable in school age children. It is the common experience that it becomes increasingly difficult to maintain strict phenylalanine control in older children but every effort should be

made to continue treatment aiming at blood phenylalanine concentrations no higher than 700 $\mu\text{mol/l}$. 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 $\mu\text{mol/l}$ 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 $\mu\text{mol/l}$ or above.

(15) Phenylalanine concentrations in pregnancy need to be at least as strictly (and probably more strictly) 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 $\mu\text{mol/l}$. 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.

1 Phenylketonuria due to phenylalanine hydroxylase deficiency: an unfolding story. *BMJ* 1993; 306: 115–9.