Late effects of phenylketonuria

Classical phenylketonuria (PKU), one of the most common inherited metabolic disorders with an incidence in the UK of approximately one in 12,000, is caused by mutations in the gene for phenylalanine hydroxylase that result in no, or almost no, enzyme activity. Individuals are unable to tolerate a standard protein intake without blood phenylalanine concentrations rising to more than 1200 μmol/l, well over 10 times the maximum level in the normal population. Without treatment, children, although healthy at birth, become severely retarded, develop microcephaly, seizures, hypopigmentation, and eczema. The natural history of this disorder has been dramatically altered since newborn screening was introduced in the late 1960s and early 1970s. The diagnosis is now made within the first weeks of life and affected children are then maintained on a phenylalanine restricted diet with amino acid, mineral, and vitamin supplements. Although the mean IQ for treated PKU patients is less than the population mean, providing blood phenylalanine concentrations are maintained at reasonable levels during childhood, patients can expect to have a normal final adult IQ. Evidence from the UK Medical Research Council (MRC)/Department of Health PKU register and elsewhere suggests that the detrimental effect of high blood phenylalanine on IQ becomes progressively less with age and after 14 years is no longer significant. However, concerns about possible consequences of persistent hyperphenylalaninaemia after childhood have led to an MRC working party recommending that phenylalanine restriction should be continued throughout life and that blood phenylalanine concentrations should be maintained at 700 μmol/l or less. This policy has major social and financial implications – for the individual with PKU, who must adhere to a difficult diet indefinitely, and for the health service which must provide the special dietary products as well as regular medical, dietary, and biochemical support. As more patients with treated PKU reach adulthood increasing resources will need to be devoted to their care.

What are the effects of PKU in adults? Probably the most important is in pregnancy: hyperphenylalaninaemia in women with PKU can cause severe fetal damage, despite the fact, as is usually the case, that the fetus does not itself have PKU. The frequency and severity of birth defects, which include microcephaly, low birth weight, and congenital heart disease, are related to the level of maternal blood phenylalanine concentration and are particularly common with concentrations above 1000 μmol/l. Fortunately there is now good evidence that, provided maternal blood phenylalanine concentrations can be kept below 360 μmol/l both before conception and during the course of the pregnancy, the outcome for the fetus is excellent. The result may be less satisfactory if biochemical control during pregnancy is not so adequate or if blood phenylalanine concentrations are reduced only after conception.

Another concern relates to the possible development of neurological deficits in adults with PKU. Despite adequate biochemical control during childhood minor neurological deficits are often found in adolescents and adults who have relaxed or discontinued their diet. These include brisk reflexes, intention tremor, delayed visual evoked responses, psychological problems, and minor impairments in cognitive abilities. The extent to which these are related to subtle neurological damage occurring in childhood or result from the effect of higher blood phenylalanine concentrations on neurotransmitter metabolism after diet relaxation is unclear but neuropsychological testing in this age group has demonstrated changes in performance related tasks which correlated with the phenylalanine concentrations. Of more concern are the reports of frank neurological illness, consisting primarily of spasticity, in a small number of older patients with PKU. When investigated these patients were found to have white matter changes on magnetic resonance imaging (MRI) of the brain and it initially appeared that these abnormalities might be directly related to the clinical illness. However, subsequent studies have demonstrated that MRI changes, involving the occipital-parietal regions and in more severe cases extending into the frontal and temporal lobes, are almost universal in older patients with classical PKU and show no relationship with the presence or absence of clinical signs nor abnormalities on neurophysiological testing.

What then is the significance of these MRI findings? The extent of white matter involvement is strongly correlated with the blood phenylalanine concentration at or around the time of imaging but is not associated with control in early childhood. Hyperphenylalaninaemia in animal studies have been associated with increased myelin turnover, decreased myelination, and defects in myelin synthesis. However, magnetic stimulation of the cortex, a technique that is sensitive to subtle changes in conditions such as multiple sclerosis, is normal in individuals with PKU and magnetic resonance spectroscopy of affected
areas of brain is not characteristic of demyelination. MRI abnormalities are at least partially reversible by reducing phenylalanine concentrations but with a lag time possibly related to the slow rate of myelin turnover in the brain. Current evidence therefore suggests MRI abnormalities do not signify demyelination but rather a reversible structural change that results in an increased water content within the myelin sheath. The functional significance of these changes remains unclear; the large majority of adult patients are not on dietary treatment and despite abnormal brain imaging remain well. Patients who have been reported with significant neurological illness have often had poor control in childhood. The risk to other patients who have been well controlled up until early teenage years remains unknown but may be very low and is probably unrelated to the change seen on MRI. Newborn screening, however, has been in operation for less than 30 years and as yet we do not have sufficient information to know whether individuals with PKU will be at increased risk from neurological disease in their fourth decade and beyond.

At present we can be sure that in order to achieve the best possible outcome for parents and their children, good biochemical control in childhood and during pregnancy is extremely important. It seems prudent to advise parents to continue a low phenylalanine diet with amino acid, mineral, and vitamin supplements into adulthood but the necessity for doing so should not be overstated to those individuals who find it difficult to comply and for those who are already off diet. Women with PKU who wish to become pregnant may find it easier to return to a very strict low phenylalanine diet if they have remained on some phenylalanine restriction and have continued taking their amino acid supplement. The diet of patients who choose not to continue phenylalanine restriction and supplements needs to be assessed to determine that it is not deficient in vitamin B12, which appears to have been the cause of a slowly progressive spastic paraparesis and megaloblastic anaemia in one patient with poor compliance.

It is clearly necessary to keep under review all patients with PKU whatever their age and sex and whether or not they choose to continue dietary treatment. Follow-up of adolescents and adults with PKU, as with children, should be in centres with sufficient numbers of patients to provide experience and expertise in their clinical, dietetic, and biochemical management. This is of particular importance for the management of women with PKU during their pregnancies. Careful monitoring of the neurological and neuropsychological status of patients as they grow older, combined with the results of continuing research, will enable us to determine more precisely the late effects of PKU and to decide whether or not the present recommendations are correct.

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