Myophosphorylase deficiency: an unusually severe form with myoglobinuria


Myophosphorylase deficiency (McArdle’s disease) is a metabolic myopathy commonly presenting with muscle cramps and fatigue in childhood. The cramps are precipitated by strenuous exercise and relieved by rest. CK levels following strenuous exercise are greatly raised. The differential diagnosis in childhood includes the myopathies (e.g., the muscular dystrophies) and other metabolic myopathies such as phosphofructokinase or lactate dehydrogenase deficiency. Evaluation of these disorders often includes muscle biopsy. After the second or third decade diagnosis of myophosphorylase deficiency is facilitated because 50% patients experience myoglobinuria owing to muscle necrosis following prolonged or strenuous exercise. The authors of this article report an unusual case of myoglobinuria in an affected 8 year old boy. In the past the classic test for diagnosis of myophosphorylase deficiency was the “forearm ischaemic exercise test” which involved measurement of preischaemic and post-ischaemic exercise venous lactate levels. This test is non-specific as metabolic blocks anywhere along the glycolytic and glycolytic pathway impair lactate production. Recently several mutations in the myophosphorylase gene have been identified in patients with McArdle’s disease with the commonest mutation being present in 75% patients with 50% being homozygous for this mutation. The reported patient with early onset of myoglobinuria and another patient with a fatal infantile myopathic variant of myophosphorylase deficiency were both homozygous for this common mutation although the authors stated that there was no consistent genotype-phenotype variation. The paper concludes that DNA analysis is now an alternative to muscle biopsy for the diagnosis of McArdle’s disease and makes biopsy unnecessary in 90% of patients. It is interesting that although the paper goes into detail about the common mutation, which is a C to T transition at codon 49 in exon 1 of the myophosphorylase gene with change of an encoded arginine to a stop codon, the authors omit to mention the chromosomal location (11q13) of the gene itself.

JILL CLAYTON-SMITH

Mutation analysis in patients with possible but apparently sporadic Huntington’s disease


Genetic counselling of families where there is an isolated case of possible Huntington’s disease can be difficult. Davis et al present 44 cases of possible sporadic Huntington’s disease studied using two polymerase chain reaction (PCR) methods. The first amplifies both the critical CAG repeat and the polymorphic flanking CCG repeat (seven to 12 copies), the second method measures the CAG repeat directly (normal range eight to 33 copies). The cases were divided into probable or doubtful Huntington’s disease. The family history was noted as negative (both parents alive or died over 65 years without suggestive features) or suspicious (for example, early death or adoption). Thirty of the 44 cases were confirmed as being affected with Huntington’s disease. Thirteen cases gave a borderline result with the first PCR method but were shown to be unequivocally positive when CAG repeat length was measured. Twenty-five of the 28 patients with probable Huntington’s disease had positive results (10 with negative family histories). Five of the 16 patients with doubtful disease were shown to have the typical expansion (two with negative family histories). In two of the patients with confirmed diagnoses and negative family histories the parent is still alive. In one, non-paternity was shown and in the other an allele in the intermediate range (35 repeats) had expanded when inherited from the father. This study provides useful confirmation that a majority of patients with typical clinical features but no family history do have Huntington’s disease. The possibility that those with negative results may have Huntington’s disease in the same gene is considered. The authors suggest that although new mutations do occur (as in one of their cases), non-paternity or mild disease which has been overlooked may be more common causes for the negative family history. Where there is doubt about the clinical diagnosis a much lower proportion of cases are shown to have Huntington’s disease. Other potential causes for chorea were present in some of their patients. A proportion of the positive results in this study had repeat numbers in the borderline range and this illustrates the importance of measuring CAG repeat length directly in cases where there is doubt about the diagnosis. This study will aid in the elucidation of the apparently sporadic cases of Huntington’s disease but, as the authors point out, the use of diagnostic DNA technology must be done with informed consent and not confused with predictive testing.

ANGELA BARNICOAT