affected pregnancies. There is a significant maternal morbidity associated with such fe-
utases from pre-eclampsia and antepartum haemorrhage so that there is a need for early diagnosis on clinical grounds leaving aside parental request because of a genetic risk. Prenatal diagnosis is available by DNA analysis or by examination of fetal haemoglobin.

In this report placental thickness was assessed in 231 pregnant women at risk of having fetuses affected with α thalassaemia 1, by transabdominal ultrasound scan at 10 to 21 weeks' gestation, when the mothers presented for invasive procedures for prenatal diagnosis. A cut off of mean placental thickness plus 2 SD was used. At gestations of less than 12 weeks this had poor sensitivity, but after this gestation sensitivity was improved although there were two false negative results (out of 184). Placental sizes were said to be large in these cases despite normal thicknesses. It is suggested that serial placental thickness measures could be used as an alternative to invasive procedures for prenatal diagnosis of α thalassaemia 1. The relative latency of diagnosis by this method and the possible occurrence of both false negative and positive results makes it unlikely to supersede current diagnostic methods. The authors suggest that in areas with a high incidence of this condition facilities for invasive prenatal diagnostic procedures may be limited and there may be a use for this method in such places. However, there will be a need for skilled ultrasonographers and suitable equipment if such a service is to be reliable.

ANGELA BARNICOAT


Maternal phenylketonuria (PKU) has been associated with microcephaly, mental retardation, congenital heart disease, and intrauterine growth retardation in the fetus. There is evidence to suggest that treatment with a phenylalanine restricted diet during pregnancy may alleviate adverse fetal effects, particularly if the diet is started before conception. Many people with a raised serum phenylalanine level have a more severe disorder than PKU. This is known as mild hyperphenylalaninaemia (MHP) and is allelic to classical PKU. MHP, when the blood phenylalanine does not exceed 600 μmol/l, is often regarded as a benign disorder as maternal phenylalanine levels of this magnitude are not considered high enough to cause either maternal or fetal effects. In this paper by Levy et al., the outcomes of treated and untreated pregnancies in two sisters with MHP are compared. The authors conclude that there have been no fetal or maternal adverse effects because of MHP in this family as both of the mothers and their three offspring had IQs within the normal range and no malformations. However, this is only a single family and as the note at the top of the paper states, “The conclusions in this article do not necessarily represent the conclusions of the Maternal PKU Collaborative Study.” In fact data from Denmark regarding offspring whose mothers had blood phenylalanine >400μmol/l, showed lower median values for birth weight, head circumference, and IQ than those with levels <400 μmol/l, although both fell within the normal range. It is also of interest that the offspring in this report who were all shown to be heterozygotes had higher IQ levels than the mothers. Therefore, although the main point of this report tells us otherwise, perhaps one should be more wary about regarding MHP as a benign disorder.

JILL CLAYTON-SMITH

Genomic organization of the Btk gene and exon scanning for mutations in patients with X-linked agamma-


These papers describe the identification of mutations causing Bruton type X linked agammaglobulinemia (XLAGGA) by gene scanning using SSCP analysis and PCR primers spanning all 19 exons of the Bruton’s tyrosine kinase gene. Hagemann et al describe the exon/intron structure of the gene for the first time. In the majority (12/14 and 25/30) of cases analysed, mutations were identified. They included single base substitutions, small deletions and insertions resulting in premature stop codons, and point mutations resulting in amino acid substitutions. No deletions larger than a few bases were found. All the mutations were family specific apart from those in exon 15, suggesting a mutation hot spot. Conley et al gauged the severity of the phenotype associated with the mutation in 15 of their cases. They also confirmed linkage to Xq22 or lack of transcription of Btk in the five cases in which no mutation was identified. Clinical diagnosis of this condition is not always straightforward as 30 to 50% of cases have no family history. There is some variability in phenotype, and about 10% of cases are females suggesting the presence of a phenocopy caused by an autosomal gene. The battery of PCR primers described in these papers will facilitate confirmation of diagnosis of XLAGGA and ascertainment of carrier status and are a considerable advance on Southern and Northern blotting techniques which can only identify a minority of mutations.

D O ROBINSON


Creutzfeldt-Jakob disease (CJD) is a mainly sporadic subacute spongiform encephalopathy with about 10% of cases being inherited as a dominant condition. The prion protein gene (encoded by the host) has been shown to have predisposing polymorphisms and pathological mutations in cases of CJD. An abnormal prion protein product accumulates in the brain of affected people. Apolipoprotein E (APOE) is produced by astrocytes in the central nervous system and is thought to be involved in lipid metabolism for repair and growth in the brain. There are three common forms of APOE coded for by specific alleles, one of which, ε4, has been shown to be associated with Alzheimer’s disease. In this study 61 patients with probable or definite CJD were genotyped for APOE by a restriction fragment length polymorphism. Cases of CJD were shown to be more likely to have ε4 APOE alleles than controls. This observation was made in both sporadic cases and in those with mutations in the prion protein gene (16 cases). The relative risk of CJD was computed between subjects with at least one APOE ε4 allele and subjects with none; it ranged between 1.8 and 4.2 depending on the control group used. The frequency of APOE ε4 allele bearers and the relative risk of CJD was the same in the sporadic group of CJD cases as in a subgroup with a specific mutation in the prion protein gene, although numbers in this group were small (11 cases). A variation in disease duration was also noted depending on APOE genotype, with an increase in duration of illness in ε2 allele carriers. There are other factors which may account for this observation, but it persisted in some groups even when the known confounding factors of age of onset and polymorphism in the prion protein gene were controlled for. APOE ε4 is shown to be a risk factor for CJD as well as Alzheimer’s disease. APOE ε2 increases the duration of CJD in patients over 65 years and has also been shown to have a protective effect against Alzheimer’s disease. The authors suggest that the isoforms of APOE may interact with prion protein produced in CJD to produce protein of an abnormal conformation. Genetic factors in the host including APOE alleles are important in the natural history of CJD, but as will notes in the associated Commentary there is yet little information on variation in the infectious agent in human spongiform encephalopathies.

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Commentary

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