Medical genetics: advances in brief

Mitochondrial DNA rearrangements with onset as chronic diarrhoea with villous atrophy

Cormier-Daire V, Bonnefont J-P, Rustin P, *et al.* *J Pediatr* 1994;124:63-70.

The list of presenting features of mitochondrial disease expands even further with this report of two patients who presented with chronic diarrhoea during the second year of life. The gastrointestinal problems, initially attributed to gluten/cow's milk protein intolerance, were severe enough to warrant parenteral nutrition in both cases. Surprisingly, in both patients, the diarrhoea remitted at the age of 4 years followed by a four to five year period of reasonable health before developing diabetes mellitus, retinitis pigmentosa, cerebellar ataxia, sensorineural deafness, and seizures. Both died at 12 years of age. The clue to an underlying mitochondrial disorder was the development of a raised plasma lactate in response to the high carbohydrate diet given because of their failure to thrive. A respiratory enzyme deficiency was recognised on skeletal muscle biopsy. Analysis of mtDNA in muscle showed that both patients had deletions in the same region of the mitochondrial genome. Lymphocyte mtDNA analysis was normal. This particular deletion has been reported before in Pearson syndrome which has quite different clinical features. The authors postulate that the high number of direct repeat sequences at the end points of the deletions predisposed to the mutations which arose de novo. Why should the cells of the gut be affected? It is suggested that it is because the cells have a high turnover rate. It remains an enigma as to why the symptoms spontaneously remitted. This paper raises the question as to whether to perform mtDNA analysis in several tissues in young children with intractable diarrhoea.

JILL CLAYTON-SMITH

Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder

Scheffer IE, Bhatia KP, Lopes-Cendes I, *et al.* *Lancet* 1994;343:515-17.

Mendelian transmission of epilepsy is unusual, although truly monogenic forms of generalised epilepsy have been successfully mapped. These authors describe the first instance of mendelian inheritance of partial epilepsy, characterised by nocturnal motor seizures. Six pedigrees are reported, with at least 39 affected cases. Previous misdiagnosis is common, although almost two-thirds of patients have secondarily generalised seizures. The age of onset varied from 0.5 to 55 years and the pattern of transmission was consistent with autosomal dominant inheritance. Intrafamilial variability of the phenotype is said to be striking and carbamazepine is the most effective therapy. There is a suggestion of clinical heterogeneity among the families reported, in that one of the six was characterised by complex partial seizures during the daytime. This family alone showed interictal EEG abnormalities. Such measures did not reveal the condition in the other five families. This latter is an important aspect, diagnosis in these families being dependent upon heightened clinical awareness. Finally, the authors highlight the resemblance to the E1 mouse model of autosomal dominant partial seizures, the locus for which is on mouse chromosome 9. Clearly the mapping studies in the six families will begin by focusing around the homologous region of human chromosome 3.

W REARDON

Characteristics of intergenerational contractions of the CTG repeat in myotonic dystrophy

Ashizawa T, 23 other authors, Harper PS. *Am J Hum Genet* 1994;54:414-23.

The discovery that myotonic dystrophy is caused by an unstable trinucleotide repeat (CTG) in the 3'UTR of a protein kinase gene, which tends to increase in size from generation to generation, appeared to fit very neatly with clinical evidence of anticipation. There have also been cases in which intergenerational contractions of the repeat have been observed, however, and the above paper summarised data from 1489 DM parent-offspring pairs from 14 centres around the world. Ninety-five pairs (6.4%) showed contractions in the triplet repeat in peripheral blood leucocytes. Sufficient clinical data were available from 56 of the 95 pairs to allow an assessment of anticipation status. Anticipation occurred in 27 (48%) of the 56 pairs, the age of onset in parent and child was similar in three (5%), and none showed a later onset of DM in symptomatic offspring, although in 26 (46%) pedigrees, children who were known to be gene carriers were asymptomatic at an age younger than the age at which their parents presented. Three of the 26 cases with asymptomatic children showed reversion of the CTG repeat size to within the normal range. In another pair, in which the ages at onset were similar, the child had a milder and more slowly progressive clinical course than that of its parent. Overall, clinical anticipation still occurred in about half of the cases with intergenerational contraction of the repeat, and in two cases the child was affected congenitally (both maternally transmitted). Contraction in repeat size occurred in 76 (10%) of 753 paternal transmissions and in 19 (3%) of 736 maternal transmission, but anticipation was proportionately more frequent with maternal transmissions (11 of 13 (85%)) than the paternal transmissions (16 of 43 (37%)). The parental repeat size correlated with the size of the intergenerational contraction. It is interesting that males, whose risk of having congenitally affected children is small, do sometimes pass on expansions that, if they had been maternally transmitted, would probably have led to congenital DM in the child. To complicate things further, congenital DM has now been reported with a large CTG repeat of paternal origin, and there is evidence that a large maternally transmitted repeat does not always result in congenital DM. Sixteen DM parents had more than one DM offspring with a contracted repeat, a higher frequency than would have been expected from the frequency of intergenerational contractions in the population as a whole. Overall, the authors conclude that (1) intergenerational contractions of the triplet repeat in DM are frequently associated with anticipation, especially when the DM is maternally transmitted; and (2) paternal origin of the repeat, and the presence of a contraction in a sib both increase the probability of CTG repeat contraction. The actual cause of clinical anticipation seems as elusive as ever.

FRANCES FLINTER

Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome

Pearson M, Hoyne E, Seaver L, Rimsza M. *Pediatrics* 1994;93:211-15.

Past reports of fetal abnormalities following occupational exposure to toluene have suggested that it may cause a specific pattern of clinical features which constitute fetal toluene

embryopathy (FTE). Toluene is a common organic solvent which readily crosses the placenta. It can be detected in the fetus as long as 24 hours after exposure because the fetus is unable to carry out the normal conversion to hippuric acid. This paper and the following one document the problems seen in a series of infants who were born after maternal solvent abuse during pregnancy. Although some infants were also exposed to other potential teratogens, a significant group was exposed to toluene alone, so that valid conclusions regarding its teratogenic potential could be drawn. Significant features noted in exposed infants were intrauterine growth retardation, microcephaly with a narrow bifrontal diameter, and facial abnormalities including short palpebral fissures, midface hypoplasia, and thin upper lip. Other features included abnormal scalp hair patterning, nail hypoplasia, and genitourinary tract abnormalities. The authors drew attention to the similarity of these features to those seen in fetal alcohol syndrome (FAS) and suggested a common aetiology, implicating increased cell death in the cells of the mesoderm ventral to the forebrain. This mesoderm rises to the frontonasal prominence which in turn goes on to form the midface structures. Increased cell death has also been shown to take place in the mesonephric ducts in FAS, tying in with the genitourinary problems. The observations confirm the potential dangers of solvent abuse during pregnancy and lead to the conclusion that both FTE and FAS are manifestations of a non-specific "fetal insult syndrome" rather than more specific diagnostic entities.

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Risks of cancer in BRCA1-mutation carriers

Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE, and the Breast Cancer Linkage Consortium. *Lancet* 1994;343:692-5.

The BRCA1 locus on 17q has previously been shown to account for the inherited predisposition to cancers in almost all families with multiple breast and ovarian cancers and approximately half of all early onset breast cancer families without ovarian cancers. The focus of this report is to provide direct estimates of the risks of breast and ovarian cancer in BRCA1 mutation carriers by establishing the risk of second cancers in patients already with breast cancer and to establish whether BRCA1 mutation carriers are at increased risk of developing cancers elsewhere. The risk of contralateral breast cancer is 48% by the age of 50 and 64% by the age of 70, giving an estimated first breast cancer risk in mutation carriers of 73% by the age of 50 and 87% by the age of 70. The ovarian cancer risk is estimated to be 29% by the age of 50 and 44% by the age of 70. In addition, there are significant excesses of colon cancer and prostate cancer among BRCA1 carriers, as well as an excess of other cancers not attributable to any single site. The relative risk of colon cancer compared with the general population is 4.11 and that of prostate cancer 3.33. This is an important paper in regard of counselling and optimal management of breast-ovarian cancer families and early onset breast cancer families. The lifetime risk of mutation carriers developing either a breast or ovarian cancer appears to be close to 100%, with a high chance of second such cancers developing. Similarly, awareness of the increased risks of colon and prostate cancers in these families are important factors in determining optimal management strategies for relevant family members.

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