Medical genetics: advances in brief

Limb defects and chorionic villus sampling: results from an international registry, 1992-94
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Commentary. Limb defects and chorionic villus sampling

Following the reports of limb defects in babies born after chorionic villus sampling (CVS) was carried out during pregnancy, the World Health Organization set up an international registry of cases. Froster and Jackson present the results of the registry for a two year period from 1992 to 1994. Seventy seven cases of limb defects were noted after CVS in a series of 21448 pregnancies (1/1738). Strict definition criteria were used for inclusion matching those used in a population survey of limb defects from British Columbia in 1993. Abnormalities consistent with recognised genetic syndromes were excluded. The pattern of abnormality was also noted and compared to that in the population study. Overall the incidence of limb defects was lower than in the population survey and there were no marked differences in the pattern of abnormality. The CVS group had fewer right sided defects and more limb defects without abnormalities in other organs, but it is suggested that these results occur because of the differing ascertainment of the data. The authors also assessed the frequency of limb defects at CVS procedures at differing gestational ages and could not show an effect of the timing of the investigation on the likelihood of limb defect occurring. As Evans and Hamerton point out in their commentary, although this seems to be reassuring news for women having CVS tests, the populations studied are not directly comparable. The CVS registry data were collected by voluntary reporting whereas the population study had cases ascertained by a number of methods. Cases in the CVS population seem to under-represent those with other major malformations and may be under-reported, incompletely described, or in pregnancies that were terminated. The issue could only be properly resolved by a large randomised trial with a direct determination of gestational age and detailed evaluation of all abnormal fetuses. The possibility of this seems remote so the question may remain unanswered. The risk of limb defects after CVS is, however, unlikely to be large and needs to be balanced against the indication for the procedure in each individual case.

ANGELA BARNICOAT

Prevalence and origin of de novo duplications in Charcot-Marie-Tooth disease type 1A: first report of a de novo duplication with a maternal origin

Charcot-Marie-Tooth (CMT), or hereditary motor and sensory neuropathy, is the commonest inherited peripheral neuropathy, and may be inherited as an autosomal dominant, autosomal recessive, or X linked disorder. CMT1, with severely slowed nerve conduction velocities, is the commonest subtype, CMT1A, in an autosomal dominant, with a locus on 17p11.2 (other loci for CMT1A include 1q21.2-q25 and Xq11.2-21.1). In the majority of CMT1 cases there is a 1-5 Mb DNA duplication on 17p11.2, and the presence of sporadic cases has been recognised since the 19th century. In order to ascertain the prevalence of de novo CMT1A duplications, the authors examined 118 duplication positive families. In 10 of these the disease was shown to have arisen as a de novo mutation, representing 8.5% of families. However, this may be an underestimate of the incidence of new mutations because of ascertainment bias: sporadic cases are less likely to be diagnosed, and some of the families studied were recruited initially because they were suitable for linkage studies. The CMT1A duplication is probably the product of unequal crossing over between parental chromosome 17 homologues during meiosis. Polymorphic markers from within the duplicated region were used to determine the parental origin of the de novo duplication in eight informative families. Seven were of paternal origin, and one of maternal origin, the first report of a de novo duplication with a maternal origin. Recombination fractions for the duplicated region are larger in females than in males, suggesting that oogenesis may have greater protection from misalignment during synapsis. However, a de novo deletion of maternal origin has been reported previously in hereditary neuropathy with liability to pressure palsies (HNPP), a clinically distinct neuropathy in which the 1-5 Mb DNA deletion occurs at the same genetic locus as CMT1A.

FRANCES FLINTER

Partial deficiency of surfactant protein B in an infant with chronic lung disease

Surfactant protein B (SP-B) is one of the components of pulmonary surfactant, a hydrophobic protein which reduces surface tension at the air-liquid interface within the alveoli. Deficiency of SP-B is a cause of death from respiratory distress syndrome (RDS) in term neonates, and gives the pathological appearances of congenital pulmonary alveolar proteinosis. Treatment for this condition is by supported ventilation or extra-corpooreal membrane oxygenation (ECMO) and then lung transplantation. Glucocorticoids and artificial surfactant have been of limited use initially in some cases. Surfactant protein B deficiency is inherited in an and the most frequent form, CMT1A, found in the SP-B gene in several affected people have now been identified. The commonest mutation is a frameshift mutation designated 121ins2. Infants homozygous for this form have presented with respiratory distress at birth. In this report, Ballard et al describe a term infant who presented with respiratory distress owing to SP-B deficiency but had a milder course than previously reported infants. He was found to be a compound heterozygote for the 121ins2 mutation and for a different mutation, R236C. He was found to have low levels of expression of SP-B, whereas the 121ins2 homoyzogotes do not express this protein. The authors conclude that there are some forms of inherited SP-B deficiency which run a milder course, with longer survival (although the long term outlook without transplantation is still not good). Expression of the SP-B gene is under developmental regulation and probably contributes to the development of RDS in premature neonates.

Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion

Friedreich's ataxia (FRDA) is an autosomal-recessive neurodegenerative disorder with a prevalence of 1 in 50 000. Onset of ataxia is typically at puberty and complications may include hypertrophic cardiomyopathy, diabetes mellitus, opathy atrophy and sensorineural deafness. Linkage to a locus on chromosome 9 (q13-q21.1) was established after a long search in 1988 and subsequently narrowed by this international team to a 130 kb internal. The results reported in this paper began with the construction of the cDNA sequence of a candidate gene X25 in which only three heterozygous point mutations were found in five out of 184 affected FRDA subjects. Southern analysis of fragments containing exon 1, however, led to the discovery of an expanded (GAA) triplet repeat tract in intron 1 of this X25 gene. Among 79 FRDA patients, all five with point mutations had heterozygos expansions, 71 had expansions on both chromosomes 9, and only three had heterozygous expansions with unidentified GAA repeat lengths. Repeat length in normal controls was seven to 22 units while the expanded alleles ranged from 200 to 900 repeats. Expanded repeats were only transmitted from asymptomatic parents of both sexes, no examples of marked expansion or reversion have been detected.
and there is little evidence of somatic mosaicism. The authors account for the drastically reduced mRNA levels of the X25 gene in FRDA patients by proposing that the intronic GAA expansion interferes with RNA processing or transcription. These results are important for a number of reasons. Firstly, the triplet repeats will provide a direct means for the diagnosis and prenatal testing of the majority of FRDA families. Secondly, they show for the first time that triplet repeat expansion is a mutational mechanism that can lead to a recessive condition, that GAA triplets as opposed to CCG, CAG or CTG triplets can be involved, and that the expansion can have an intrinsic location. Thirdly, they suggest that the phenomenon of anticipation need not invariably be associated with triplet repeat mutations. It will also be possible to consider whether repeat length is correlated with age of onset or the expression of the less common FRDA complications and whether alterations of the FRDA gene and its protein product frataxin might have a wider role in the etiologic complexity of heart disease or diabetes.

JOHN C K BARBER

Prenatal screening for cystic fibrosis: 5 years' experience reviewed

Professor Brock reviews his five years' experience of offering cystic fibrosis (CF) testing to couples who present to the antenatal clinic. Two models of testing were used, either a two stage process, where the mother was tested first and testing only offered to her partner if she was shown to be a carrier, or a couple procedure where both partners were tested simultaneously. A total of 25000 couples were screened over the five year period. Uptake was similar in both models at about 70%. Twenty two couples were identified with both partners detected as being carriers; 20 of these opted for prenatal diagnosis and termination of eight affected fetuses was carried out. No information is available as to whether any affected babies were born whose parents were not detected as being at risk, either through the technical limitations of screening for selected mutations, or through late presentation in pregnancy, or through a decision not to participate in the programme. Professor Brock concludes from the results that couple testing has proved the better option for prenatal screening for CF. Although in the two stage model testing can be offered to relatives of all those women identified as carriers, in practice the uptake of this has been low. The couple testing method reduces the number of counselling sessions needed and raises anxiety only in those couples with a 25% risk of an affected fetus. The study has shown consistent high levels of take up of screening with both models, even when research has moved to service provision, and confirms the interest of the population in genetic testing when directly related to their own reproduction.

ANGELA BARNICOAT

Non-Mendelian transmission in dentatorubral-pallidoluysian atrophy and Machado-Joseph disease: the mutant allele is preferentially transmitted in male meiosis

Over the last 10 years geneticists have come to terms with several patterns of inheritance which do not follow a simple mendelian pattern. In this report, from Niigata University in Japan, the authors report a skewed form of autosomal dominant inheritance with preferential transmission of the mutant allele in male meiosis. Two CAG triplet repeat disorders, dentatorubral-pallidoluysian atrophy (DRPLA) and Machado-Joseph disease (MJD), have been studied. As expected, there was an inverse correlation of age at onset with the length of the expanded CAG trinucleotide repeats, and the intergenerational instability of the length of the CAG repeat was more prominent in paternal transmissions (these factors appear to explain clinical evidence of anticipation). The segregation patterns were studied in 211 transmissions in 24 DRPLA pedigrees, and 80 transmissions in seven MJD pedigrees. Significant distortions in favour of transmission of the mutant allele were found in male meiosis, where the mutant alleles were transmitted to 62% of offspring in DRPLA, and 73% in MJD (both reaching statistical significance). The authors suggest that the results are consistent with meiotic drive in DRPLA and MJD in male meiosis, and since more prominent meiotic instability of the length of the CAG repeat is observed in male meiosis as well, the authors postulate that a common molecular mechanism may underlie both phenomena. Studies of this kind may be subject to ascertainment bias, but from a practical point of view, if these findings are confirmed elsewhere, clinicians may have to increase the risk quoted to offspring of inheriting DRPLA or MJD if the affected parent is the father. A prior risk of greater than 50% of inheriting an autosomal dominant disease is likely to have a significant impact on genetic counselling.

FRANCES FLINTER