Medical genetics: advances in brief

Congenital bilateral absence of vas deferens in the absence of cystic fibrosis

Augarten A, Yahav Y, Kerem BS, *et al.* *Lancet* 1994;344:1473-4.

The frequency of cystic fibrosis mutations in a group of infertile males with congenital bilateral absence of the vas deferens was studied by Augarten *et al.* They divided their study population of 47 males into two groups. One group of 10 males (21%) had associated renal malformations (unilateral agenesis in all cases, with some of the single kidneys being ectopic). The other group of 37 males (79%) had normal ultrasound examinations of the renal tract. All patients were screened for nine cystic fibrosis mutations common in the study population. Two of the study group were shown to be affected with cystic fibrosis and 16 to be heterozygous for one cystic fibrosis mutation. All of those with one or more cystic fibrosis mutation fell into the group without renal malformations, and of this group 18/37 (49%) were at least heterozygous for cystic fibrosis. Three further patients in this group had an abnormal sweat chloride level although no mutation was identified. Sweat chloride levels were normal in all patients where there were renal malformations. Augarten *et al.* suggest that congenital bilateral absence of the vas deferens is a heterogeneous condition and only a proportion of affected males have a form of genital cystic fibrosis. They propose that genetic counselling for cystic fibrosis can be omitted in such patients with renal malformations. Further data on similar patients would be desirable before implementing this strategy.

ANGELA BARNICOAT

Association between X-linked mixed deafness and mutations in the POU domain gene POU3F4

de Kok YJM, van der Maarel SM, Bitner-Glindzicz M, *et al.* *Science* 1995;267:685-8.

Severe congenital deafness is distressingly common in children with a frequency as high as 1 in 1000 births. Among non-syndromic families, an autosomal recessive form has been linked to proximal 13q, an autosomal dominant form to 5q31, and the most frequent X linked type (DFN3), which is associated with stapes fixation, to Xq21. Noting that the murine transcription factor *Pou3F4* had been mapped to a homologous region in mouse and was expressed in brain, neural tube, and otic vesicle in the rat embryo, this team used amplified fragments from the murine gene to confirm that the human homologue lay within a single cosmid contig from the DFN3 region. Human POU3F4 fragments were then used to screen a human fetal brain cDNA library which yielded six cDNAs from which a 1083 bp coding region was deduced. SSCP analysis showed mutations in 5/14 (36%) patients with X linked deafness of whom three had deletions leading to premature stop codons and two had missense mutations within the conserved POU homeo-domain which is thought to be vital for binding to the DNA major groove. In one of the deletion families the mutation cosegregated with deafness in seven affected males. To the authors' surprise, POU3F4 was not included (nor mutated) in three families with molecular deletions or a duplication of Xq21 raising the possibility of regulatory mutations, position effects, or a second locus.

However, as at least five POU domain genes are expressed in the developing inner ear and it seems likely that the candidate gene approach will provide further insights into the cause of X linked deafness in those 9/14 patients in whom no POU3F4 mutations can be detected.

JOHN BARBER

Bone marrow transplantation for autosomal recessive osteopetrosis

Gerritson EJA, Vossen JM, Fasth A, *et al.* *J Pediatr* 1994;125:896-902.

Autosomal recessive osteopetrosis is a rare disease of infancy caused by defective osteoclastic bone resorption. This gives rise to increased bone density and skeletal mass, defective haemopoiesis, and progressive neurological impairment. Compression of the optic nerve leading to visual impairment is a common feature. Untreated, death usually occurs before the age of 5 years. The basic cellular defect in osteopetrosis is unknown, except for a small subgroup with carbonic anhydrase II deficiency. Medical treatments have included the use of corticosteroids, parathormone, calitriol, and gamma interferon. Surgical decompression of the optic nerve can be performed. However, bone marrow transplantation is the only method by which osteoclast function can be restored on a permanent basis. In this article the Working Party on Inborn Errors of the European Bone Marrow Transplantation Group report the clinical outcomes of 69 patients who have undergone BMT for osteopetrosis between 1976 and 1994. Data from 12 centres including three in the UK were presented. The median age for BMT was 3 months and 30/69 patients were still alive. The main causes of death were graft failure and the toxic effects of marrow ablation. Five of the 30 survivors did not develop any osteoclastic function following BMT. The remaining 25 patients had detectable osteoclastic function and there was a magical "clearing of bone" on x ray as a result. There was also reduction in the size of the liver and spleen, and catch up growth in some patients. Vision improved in 2/16 visually impaired patients and remained static in the remainder, some of whom were blind and needed special schooling. Development was normal in long term survivors. One patient who showed evidence of neurodegeneration pre-BMT continued to deteriorate and died four months post-transplant, although he may have had a rare familial variant of osteopetrosis as opposed to the "regular" form. One common complication was that of hypercalcaemia owing to bone resorption. Patients fared much better if they had an HLA identical transplant rather than a mismatched graft (79% five year survival compared with 38% with one mismatch). Although these results are encouraging, only 12% of the original patient group were alive with no significant disabilities at follow up and the authors comment that the decision to perform a BMT remains an ethical dilemma. The presence of osteopetrosis has been observed in mice lacking the SRC proto-oncogene and the C-fos gene and in those with a defect in the gene encoding macrophage colony stimulating factor. Although none of these has yet been shown in humans examination of mouse models could provide a clue to the defect in man and ultimately to more successful treatments.

JILL CLAYTON-SMITH

Maternal mild hyperphenylalaninaemia: an international survey of offspring outcome

Levy HL, Waisbren SE, Lobbregt D, *et al.* *Lancet* 1994;344:1589-94.

Maternal phenylketonuria (phenylalanine levels >720 µmol/l) is recognised as a cause of intrauterine growth retardation, microcephaly, and mental retardation in babies, as well as of other fetal malformations including cardiac defects. Levy *et al.* investigated the effect of raised phenylalanine levels (in the range of 180-720 µmol/l) in mothers on their babies. Eighty six mothers who had 219 pregnancies were identified retrospectively by questionnaires sent to doctors. Further details regarding the mothers' intelligence, method of ascertainment, phenylalanine level (including details of the assay used to measure the phenylalanine), and on the outcome of the pregnancies was obtained again by questionnaire; where data were incomplete referring physicians were contacted to obtain the relevant information. Only pregnancies where the mothers had been on an unrestricted diet were included. The median maternal phenylalanine level was 410 µmol/l. The mothers were mostly of normal intelligence with none reported as being mentally handicapped. There was no increase in pregnancy complications in the study population when compared to general population data. Thirteen percent of the offspring were reported as being affected with phenylketonuria (phenylalanine levels >776 µmol/l) and were having dietary treatment. Four children (2.3%) had congenital heart disease which is within the 95% confidence interval for the general population. Five children (2.9%) had other severe abnormalities, a level closely similar to that of the general population. The median birth weight and length was on the 50th centile, but the median head circumference at birth was only on the 25th centile. There was some evidence that women with higher levels of phenylalanine were more likely to have small babies. The information on the development of the children was incomplete (data on 108/173) but did not clearly indicate any deviation from normal, although the IQs of babies born to women with higher phenylalanine levels (>400 µmol/l) were significantly lower than the rest of the study group. Levy *et al.* report that the relationship between maternal phenylalanine level and IQ is confounded by maternal IQ and suggest that either the raised phenylalanine level has exerted the same toxic effect on both mother and child, or that the lower IQ is the result of postnatal environment. They suggest that the reduced head circumferences along with the data on development do indicate some effect of the raised phenylalanine on fetal brain growth at higher levels. Their sample produced a higher proportion of infants affected with phenylketonuria than would be expected from an unbiased sample. This study has not provided conclusive evidence for the need to intervene in the pregnancies of women with any degree of hyperphenylalaninaemia. Such a policy would be expensive in terms both of identification of women at risk and of monitoring and managing them during pregnancy. There is sufficient evidence to be concerned particularly where the level of maternal phenylalanine is greater than 400 µmol/l; data from further studies may help to clarify the issue.

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