Medical genetics: advances in brief

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


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, with POUS3F4 mutations, 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 population study. 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 mutations fell into the group without renal malformations, and of this group 18/37 (49%) were at least heterozygous for cystic fibrosis. Three further studies in this group had an abnormal sweat chloride level although no mutation was identified. Sweat chloride levels were normal in all patients with POUS3F4 mutations. 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 POUS3F4 mutations. Further data on similar patients would be desirable before implementing this strategy.

ANGELA BARNICOCAT

Association between X-linked mixed deafness and mutations in the POU domain gene POUS3F4


Severe congenital deafness is distressingly common in children with a frequency as high as 1 in 1000 births. Among non-syndromic familiy deafness cases, POUS3F4 has been linked to proximal 13q, an autosomal dominant form to 5q31, and the most frequent X linked type (DFNS), 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 POUS3F4 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 which 12 lesions leading to premature stop codons and two had missense mutations within the conserved POU homeodomain which is thought to be vital for binding transcription factors. One major proportion of the deletions deleted parts of the deletion families the mutation co-segregated with deafness in seven affected males. To the authors’ surprise, POUS3F4 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.

JILL CLAYTON-SMITH

Maternal mild hyperphenylalaninaemia: an international survey of offspring outcomes

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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 yield insights into the cause of X linked deafness in those 9/14 patients in whom no POUS3F4 mutations can be detected.

JOHN BARBER

Bone marrow transplantation for autosomal recessive osteopetrosis


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 compression of the optic nerve leading to visual impairment. A common feature. Untreated, death usually occurs before the age of 5 years. The basic cellular defect is the osteoclast, except for a small subgroup with congenital anhydrolyse II deficiency. Medical treatments have included the use of corticosteroids, parathormones, vitamin D, 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 narrow 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 spectacles. 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 (75% 5 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 where a C-fos gene encodes an osteoclastogenesis macrophage colony stimulating factor. Although none of these has yet been shown in humans examination of mouse models could provide a unique tool to the defect in man and ultimately to more successful treatments.

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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 newborn infants who had 219 pregnancies were identified retrospectively by questionnaires sent to doctors. Further details regarding the mothers’ intelligence, method of ascertainment, and phenylalanine level (including details of the assay used to measure the phenylalanine), and on the outcome of the pregnancy was obtained against a questionnaire; where data were incomplete referring physicians were contacted to obtain the relevant information. Only pregnancies where the mothers were on unrestricted diet were included. The median maternal phenylalanine level was 410 μmol/l. The mothers were mostly of normal intelligence with none 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), which were having dietary treatment. In children (2.3%) had congenital heart disease which is within the 95% confidence interval for the general population. Five children (0.7%) had severe developmental delay, one 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, and catch up growth in some patients. Weight increased in 2/16 visually impaired patients and remained static in the remainder, some of whom were blind and needed spectacles. 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 (75% 5 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 where a C-fos gene encodes an osteoclastogenesis macrophage colony stimulating factor. Although none of these has yet been shown in humans examination of mouse models could provide a unique tool to the defect in man and ultimately to more successful treatments.

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