Allogenic bone marrow transplantation for lysosomal storage diseases


Bone marrow transplantation has been used for about 10 years to treat patients with inherited lysosomal storage disorders. This report is a retrospective analysis of 63 such patients to assess the benefits of this therapy. The transplants were done for a variety of conditions and in a number of centres although very similar protocols were used in all cases. The mortality from the procedure itself was 10% if an HLA identical sib donor was available, and two to three times this if an unmatched donor was used. Follow up after a successful transplant was available on only 28 of the original cohort; for the remainder there was either transplant rejection, transplant related mortality, or follow up of less than one year. There was good evidence that the expression of some clinical features after transplantation, particularly of visceromegaly, there was little or no progression of other symptoms, such as skeletal problems, during the period there was significant neurological deficit before transplantation, it was likely that there would be disease progression. The potential mechanisms of bone marrow transplantation to benefit this group of patients are the replacement of macrophages laden with storage product with enzymatically competent cells, the transfer of normal enzyme to other cells and into the plasma, and the clearance of storage product from the tissues because of the reduced levels in the circulation. As Warkany and Dobrenis suggest in their commentary, there are few data to suggest that replaced enzyme will be able to cross the blood brain barrier, and further doubts about what the potential benefits of bone marrow transplantation may be influenced by the disease process and the pathological sequelae of the metabolic defect may not be readily reversed. The study by Hoogerbrugge et al is hampered by small numbers in each disease category and incomplete data on follow up, but does seem to show that clinical experience bears out these uncertainties, and that in particular there is little evidence for neurological benefit in bone marrow transplantation for patients with lysosomal storage disorders.

**ANGELA BARNICOAT**


Deletions of 5p are associated with a contiguous gene syndrome known as the cri du chat syndrome, because of the characteristic cat-like cry with which patients present at birth. The syndrome may include failure to thrive, microcephaly, hypertelorism, epicanthic folds, hypotonia and severe mental retardation. The authors of this report have studied 10 families in which patients with 5p– have the cat-like cry in isolation, or just in association with mild developmental delay. They used FISH to determine the precise location of the deletions in each family, and found that all the deletion breakpoints in their four families lay distal to the chromosomal region implicated in the full blown syndrome described previously, in which patients have the characteristic dysmorphic features and severe developmental delay. DNA clones mapping to the chromosomal region associated with the cat-like cry will be useful diagnostic tools, enabling distinction between 5p deletions involving 5p15.2, which will result in severe developmental delay (as observed in most cri du chat syndrome patients) and smaller deletions restricted to 5p15.3, which result in the isolated cat-like cry, associated with a much better prognosis.

**FRANCES FLINTER**


In recent years increased attention has been focused on the identification of specific “behavioural phenotypes” in different chromosomal and other genetic syndromes. Of these, fragile X syndrome has perhaps been the most extensively studied. This paper reports the findings of a multidisciplinary team from Baltimore comprising neurogeneticists, psychiatrists, and paediatricians. They carried out a comprehensive phenotypic study of 31 males with fragile X syndrome and 30 age, sex, and IQ matched controls. The Vineland Adaptive Behaviour Scales and the Aberrant Behaviour Checklist, which are both well established instruments for measuring behaviour profiles, were used and both parents and teachers participated in the study. The number of CCG repeats within the FMR1 gene was recorded in each case. The results were analysed using a myriad of statistical analyses, and a distinctive pattern of aberrant behaviour among males with fragile X syndrome, which was different from the aetiological heterogeneity control group of males of the same age and developmental level, emerged from the study. Fragile X males were more hyperactive and distractible than the controls. They tended to talk excessively and talk to themselves in a greater extent than controls, frequently repeating words and phrases. They had repetitive, stereotyped movement of the hands, arms, and body but did not display self-injurious behaviour. On the Vineland scale, which assesses adaptive behaviour with regard to communication, socialization and daily living skills, no characteristic pattern was seen in the fragile X males, though they did rate higher than normal on daily living skills and other two domains. More fragile X subjects met diagnostic criteria for attention deficit hyperactivity disorder, stereo-typy-habit disorder, and for past or present autistic disorder. There was no linear association between the size of the fragile X amplification and the phenotypic profile. These findings extended those of previous reports and have implications for the purposes of such a study as helping to elucidate the neurodevelopmental pathways of normal behaviour and psychopathology, aiding design of screening tests for this syndrome, and aiding research into the interface of interventive strategies. They suggest that the fragile X mutation may have specific effects on brain development and function in the areas which mediate behavioural inhibition or self-regulation. It is important to recognise, however, that many of the behavioural characteristics noted, for example, hand flapping, hyperactivity, and excessive talking, have been reported in patients with the behavioural phenotype of other syndromes such as Angelman and Williams syndromes and care must be taken before attributing the behaviours to a specific effect of the FMR1 gene. We are now becoming aware that recognition of the behavioural phenotype can aid diagnosis of many disorders. For the clinical geneticist involved in diagnosis, direct microsatellite instability, also generates mutations in the coding sequence of one of two transforming growth factor-β (TGF-β) receptor genes. Normally the products of these genes form a homeric complex which ensures that signals from TGF-β isoform inhibit epithelial cell proliferation. In 12/38 human colon cancer cell lines, however, a ribonuclease protection assay showed a marked reduction or absence of type II receptor transcript. This reduced expression was found in 9/11 cell lines with microsatellite instability and only 3/27 cell lines without. No TGF-β binding was detected in cell lines with reduced expression. Subsequently three different frameshift mutations were detected in seven of the cell lines with reduced expression and microsatellite instability. All three mutations had removed one or two bases from a short repetitive sequence of 10 adenines in the 5’ half of the type II gene leading to a truncated protein. The presence of the mutations in original tumour material and not in normal tissue was confirmed. The cell lines were derived from a variety of colon cancer sources including two HNPCCs and five with DNA repair gene mutations. Progression from constitutional mutation through microsatellite instability and receptor gene mutations to the proliferation of epithelial cells released from growth inhibition is an attractively direct model for the development of some colon cancers. One immediate practical consequence is that it and the possible testing screen for a variety of cancers by looking for type II TGF-β receptor mutations in stools.

**JILL CLAYTON-SMITH**


One of the most intriguing recent findings in cancer genetics was the discovery that predisposing mutations in no less than four genes involved in DNA repair are responsible for the inherited element of hereditary non-polyposis colon cancer (HNPCC) while short repetitive DNA sequences (microsatellites) from HNPCC tumours frequently show variation. Inactivation of the type II TGF-β receptor.

**JOHN K BARBER**