Medical genetics: advances in brief

Canavan disease: from spongy degeneration to molecular analysis

Matalon R, Michals K, Kaul R. *J Pediatr* 1995;127:511-17.

Canavan disease is a progressive leukodystrophy with clinical features of severe mental retardation, macrocephaly, and spongy degeneration of the brain. It is especially prevalent among the Ashkenazi Jewish population. The basic defect leading to Canavan disease was discovered in 1988 and shown to be a deficiency of the enzyme aspartoacylase, leading to increased urinary excretion of N-acetylaspartic acid (NAA). The diagnosis can therefore now be made on blood or urine examination without resorting to brain biopsy. More recently, the human gene for aspartoacylase has been cloned and localised to chromosome 17p13. NAA is synthesised in brain cells and appears to have a role in the maintenance of healthy white matter. The role of NAA in other conditions, such as Alzheimer's disease and Huntington's disease, is also currently under investigation. This article is a comprehensive review of Canavan disease based on the experience of 165 patients known to the authors. The main clinical features comprise the triad of hypotonia, head lag, and macrocephaly, with symptoms first becoming apparent at 3 to 6 months. Feeding difficulties are common, with seizures and optic atrophy developing in the second year of life. Inability to support the head remains a constant feature with age. Neuroimaging studies show diffuse, subcortical white matter degeneration and the brain atrophies with progression of the disease. Differential diagnosis includes Alexander disease, metachromatic leukodystrophy, Tay-Sachs disease, and cerebral palsy in older children because of the spasticity which develops. Most of those affected die within the first decade although life spans from 1 to 32 years have been reported. Some argue, therefore, that there are separate congenital, infantile, and juvenile forms, although it is not yet known how these correlate with the specific mutations found. Molecular studies show that two specific mutations account for 97% of the alleles in Ashkenazi Jewish patients with Canavan disease, whereas in non-Jewish patients the mutations were different and more diverse. In the series of patients reviewed, approximately 60% were of Jewish origin. Carrier testing by biochemical methods is difficult, but with a carrier frequency of 1 in 37 in the Ashkenazi Jewish population and the availability of a

useful molecular genetic test, this may be one more condition for which carrier screening is merited.

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Prognostic implications of fetal echogenic bowel

Slotnick RN, Abuhamad AZ. *Lancet* 1995; 347:85-7.

The likelihood of cystic fibrosis (CF) following detection of echogenic bowel on prenatal ultrasound examination without a prior risk is not well defined. Slotnick and Abuhamad attempt to resolve this by grading the severity of the bowel changes into three grades, by comparison of the sonodensity with the fetal iliac crest. The findings were confirmed by two investigators. A total of 7400 pregnancies were scanned in the second trimester and 145 were identified as having echogenic bowel. All were offered genetic counselling, parental CF carrier testing, and amniocentesis if appropriate. Forty fetuses had mildly increased echogenicity of the bowel. Postnatal information on 33 of the babies suggested no cases of CF or chromosome abnormality. Eighty one pregnancies had a moderate degree of bowel echogenicity. Two fetuses were shown to be affected with CF and two cases of trisomy 21 were detected. Follow up information was available on 79 pregnancies; no other abnormalities were detected. Twenty four fetuses had bowel with a high degree of echogenicity. Information was available on the outcome of 22 of these pregnancies. Five of these 24 pregnancies were shown to be affected by CF either during pregnancy or postnatally. Six pregnancies were affected with Down syndrome. The authors suggest that their method of quantifying the sonodensity of the fetal bowel enables those at higher risk of CF and karyotype abnormalities to be detected. Although grading of the severity of echogenic bowel does seem to help in identifying those pregnancies at higher risk of CF, the diagnosis is not considered until the second trimester with the attendant anxiety about late testing and decision making during pregnancy. Even in those fetuses with the most severe degree of echogenic bowel, about half did not have an abnormality detected and resulted in the birth of healthy infants.

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Screening the 3' region of the polycystic kidney disease 1 (PKD1) gene reveals six novel mutations

Peral B, San Millan JL, Ong ACM, et al. *Am J Hum Genet* 1996;58:86-96.

Autosomal dominant polycystic kidney disease (ADPKD) affects about 1 in 1000 people. In 85% of cases it is caused by mutations in a gene on chromosome 16, and in 15% by mutations in a gene on chromosome 4. The average age of renal failure in the former (PKD1) is 56 years, and the fact that the gene shows reduced penetrance on ultrasound scan below the age of 30 years means that there is a demand for a definitive presymptomatic test. In addition, the difficulties which occur sometimes in the interpretation of a finding of polycystic kidneys antenatally means that there would be several uses for a molecular test. The gene for PKD1 was mapped to chromosome 16 in 1985 and cloned in 1994. Since then, full characterisation of the PKD1 gene has been completed recently, with the entire sequence of the transcript and the genomic region containing the gene determined. The PKD1 gene covers 52 kb of genomic DNA and is divided into 46 exons. The transcript is ~14-15 kb, and the predicted protein, polycystin, consists of 4302 amino acids. The structure of polycystin indicates that it plays a role in cell-cell or cell-matrix interactions. Cloning the full length PKD1 transcript and the search for mutations were complicated because most of the transcript is encoded by a genomic region duplicated elsewhere on chromosome 16. During the last year, seven small mutations have been identified, mostly at the 3' end of the gene in the single copy area, in addition to some longer deletions (sometimes involving the TSC2 gene). In the current study, the authors screened systematically most of the translated, single copy, 3' part of the gene for subtle mutations. They found six novel mutations, two deletions, an insertion of a T-nucleotide causing a frameshift, two single base pair substitutions resulting in premature stop codons, and a G→C transversion which may be a missense mutation. In total, the mutation detection rate is now 10-15%, and, unfortunately, the results indicate that the majority of mutations lie within the duplicated area, which is difficult to study. Genotype-phenotype correlations indicate that, so far, there is no obvious clinical difference between patients with large frameshifting or terminating changes, and more subtle in frame changes.

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