Medical genetics: advances in brief

A multiinstitutional survey of Wiskott-Aldrich syndrome

Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. *J Pediatr* 1994;125:876-85.

Wiskott-Aldrich syndrome is an X linked disorder giving rise to thrombocytopenia, eczema, and immunodeficiency. Clinical diagnosis is difficult because not all patients have this characteristic triad of features and the phenotype varies, even within a single family. In this paper Sullivan *et al* report the results of a large survey within the US in which clinical and laboratory data were collected on 154 affected subjects. Thirty-four physicians were involved in this study, the aim of which was to define the clinical spectrum of WAS and learn more about the natural history of the disorder. Seventy four of the patients had a family history of the disorder but the majority were sporadic cases. Thrombocytopenia was a prerequisite for entry into the study but only 27% of patients had the typical triad of symptoms originally described by Aldrich. The immunological findings in particular varied considerably with the most distinctive finding being a low CD8+ count in 61%. Eczema developed in 81% at some stage but was not always present at diagnosis. In those patients where platelet size was measured it was always small, although it increased following splenectomy. The average age at diagnosis was 21 months and at death was 8 years. There were, however, 16 patients who lived beyond 18 years and the prognosis for the disorder has improved considerably in recent years. Bone marrow transplantation was carried out in 47 cases with a good outcome in two thirds of cases. Infections were the result of both humoral and cellular immune deficiency with otitis media, diarrhoea, and pneumonia being the most common. Forty percent of patients had autoimmune disorders and this group had a poor prognosis as they were more likely to develop a malignancy. Malignancies were seen in 13% of patients and were mainly of the lymphoreticular system. The authors conclude that many patients with Wiskott-Aldrich syndrome have an atypical presentation. The diagnosis in the study cases was made purely on clinical grounds. Now that the molecular defect in some WAS families has been identified it will be interesting to see if the clinical observations are borne out by molecular studies, particularly in the sporadic cases who outnumbered the familial cases, and in the patients with autoimmune disease and a predisposition to malignancy who appear to form a separate subset.

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Mutations in the gene for X-linked adrenoleukodystrophy in patients with different clinical phenotypes

Braun A, Ambach H, Kammerer S, *et al.* *Am J Hum Genet* 1995;56:854-61.

X linked adrenoleukodystrophy (X-ALD) affects 1 in 15 000 to 1 in 20 000 white

males and is the commonest peroxisomal disorder. It causes severe, progressive demyelination of the white matter and adrenal cortex insufficiency. The biochemical abnormality is impaired peroxisomal β oxidation of unbranched, saturated, very long chain fatty acids (VLCFA) in most tissues. There is marked phenotypic variability, however, even within families. The three most common phenotypes are cerebral childhood ALD (43%), adrenomyeloneuropathy (AMN) (26%), and Addison's disease only (ADO) (11%). In addition, 7% of affected males with raised VLCFA have normal neurological and adrenal function. Recently a gene encoding a peroxisomal membrane transporter protein was isolated by positional cloning, and intragenic deletions were detected in some ALD patients. Braun *et al* analysed the entire protein coding sequence of the gene by reverse transcription PCR, SSCP, and DNA sequencing in five patients and their female relatives. In the three patients with classic, severe ALD they identified in the 5' end of the gene a 38 bp deletion causing a frameshift mutation, a 3 bp deletion causing an amino acid deletion in the ATP binding domain of ALD protein, and a missense mutation. The patient with AMN had a nonsense mutation in codon 212, and a single base change in exon 178 which caused a glutamine to glutamine acid substitution at a non-conserved amino position. The patient with ADO had a single point mutation (G to A) causing an arginine to histidine substitution in a highly conserved position. These mutations were detected in the heterozygous state in the four mothers who were available for study, and carrier testing was performed successfully in sisters. This is important because biochemical carrier tests in females have a 15% false negative rate. Considerable intrafamilial variation is a well recognised phenomenon in X-ALD, with some pedigrees having examples of all three phenotypes. Moser has suggested that it is more likely that an autosomal modifier gene is responsible for the variable expression of the disease than environmental factors, having observed Mendelian segregation of the clinical phenotypes in pedigree analyses. Linkage analysis with discordant affected sibs may be informative. Intrafamilial variability of an X linked disease excludes allelic variation or compound heterozygosity as causes for clinical heterogeneity; however, there might be an interaction among mutations in different genes. A candidate gene could be the PMP70 gene as the deduced amino acid sequence of the ALD protein shows a 70% homology with a 70 kDa peroxisomal membrane protein PMP70. (Both the PMP70 and the ALD proteins belong to the "ATP binding cassette" superfamily of membrane transport proteins.) Alternatively, it is possible that there may be an unidentified mutation in the gene for VLCFA-CoA synthetase which could contribute to the variable expression of the disease. Another theoretical possibility is the existence of a modifier gene encoding a protein

capable of protecting different tissues against high levels of VLCFA. Certainly further understanding of this complex disease at a molecular level may provide a better understanding of the biological interactions of peroxisomal membrane transporters, and ultimately, perhaps, clues for the development of new treatments.

FRANCES FLINTER

Comparison of women who do and do not have amniocentesis or chorionic villus sampling

Halliday J, Lumley J, Watson L. *Lancet* 1995; 345:704-9.

Chorionic villus sampling or amniocentesis to determine fetal karyotype is free to all women of 37 years or more in the state of Victoria, Australia. An increasing number of mothers in this population are in this age group, and although the number of prenatal tests has increased, the increase has not been in proportion to the number of older mothers. The uptake of tests and the possible reasons for women not having a test are examined in this study. Data on all testing procedures where the indication was raised maternal age were matched with information on completed pregnancies. The collection of these data is centralised and virtually complete. Information on a total of 7111 pregnancies was assessed. A number of factors were identified as reducing the likelihood that a prenatal testing procedure would be performed (in order of importance): high parity, mother born in non-English speaking country, delivery in public hospitals or especially at home, absence of any previous termination of pregnancy, and inhabitation of rural areas. The authors suggest that the main reason for low uptake in women of high parity is religious beliefs. An attempt to test this hypothesis by looking at interaction between high parity and country of origin does not help resolve this. The study does suggest that there are problems of access to testing in certain groups, such as those who originate from non-English speaking countries and those who live in rural areas. The uptake of testing in the study population is lower than in previous studies (43% of 37 to 39 year old women did not have a test). This study cannot show whether this is because of the informed choice of mothers not to be tested, or whether poor access and information restrict testing; however, interesting demographic characteristics of tested and untested groups are shown. As maternal age becomes superseded by maternal serum screening as a criterion for offering a prenatal test, changes in the uptake of the screening test and of a prenatal test in those identified as being at high risk will be important to study.

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