Wiskott-Aldrich syndrome: a multidisciplinary disease

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Introduction

Wiskott-Aldrich syndrome is a rare X-linked disorder which, in its fully expressed form, is recognised by the clinical triad of combined immune deficiency, thrombocytopenia, and eczema.¹ An increased risk of malignancy has also been reported, with an incidence of about 12% in some series and susceptibility, in particular, to acute leukaemia, lymphoma, and solid tumours of the central nervous system.² Other less common manifestations include asthma, autoimmune haemolytic anaemia, arthritis and glomerulonephritis. Because of the combined risks of serious infective complications, bleeding and malignancy, survival to adulthood is rare. There is some optimism for the future prospects of patients with the syndrome and their families, however, as a result of recent advances in the molecular biology and genetics of the disorder and parallel developments in clinical management.

Immune deficiency

The immune deficiency in Wiskott-Aldrich syndrome takes various forms, but in severe cases both humoral and cell mediated immunity are impaired. Abnormalities of serum immunoglobulins with increased IgA and IgE and depressed IgM are characteristic and transient paraproteinaemias are occasionally observed.^{3,4} Affected males commonly fail to respond to challenge with polysaccharide antigens and in many cases the B cell dysfunction leads to a pronounced susceptibility to severe infections with encapsulated organisms including *Pneumococcus*, *Staphylococcus*, and *Haemophilus*.⁵ This is manifest clinically by recurrent otitis media, skin abscesses, and sinusitis with intervening episodes of potentially fulminant pneumonia, meningitis, and septicaemia. Even in patients with attenuated variants of the syndrome, and few infective complications, polysaccharide isoagglutinins may be absent or reduced in titre and this can be a useful diagnostic marker.⁶

Abnormalities of cell mediated immunity tend to increase in severity with age, and disseminated viral and fungal infections are commonly found. Patients may show poor responses to in vivo challenges with T cell dependent antigens, absent delayed hypersensitivity on skin testing, and impaired lymphocyte responses to mitogens and allogeneic cells.⁷ Changes in T cell subsets with a reduced number of CD4 positive cells and increased circulating non-mixed histocompatibility complex restricted cytotoxic cells or

CD16 positive natural killer cells are frequently observed.⁸ Transformed B lymphoblastoid cell lines from affected patients show normal responses to the B cell growth factors IL-4 and IL-6⁹ and it seems likely that the immune deficiency in the syndrome is due to a primary T cell defect. This view is supported by the observation that humoral immunity has been restored in recipients of allogeneic marrow transplants which have become T cell chimeras in the absence of haemopoietic engraftment.¹⁰

The primary biochemical defect in the syndrome has yet to be identified but increasing evidence suggests that it is in some way related to impaired expression of a heavily glycosylated acidic glycoprotein termed sialophorin (CD43).¹¹ A distinctive structural feature of this surface glycoprotein is its high content of sialylated O-linked disaccharide units and it has been found to be widely distributed on all circulating mononuclear cells, granulocytes, and platelets. In early studies Remold-O'Donnell and colleagues showed that sialophorin was absent, reduced, or in an abnormal high molecular weight form on the lymphocytes of patients with the syndrome.^{12,13} CD43 antibodies stimulate T cell proliferation and promote the secretion of IL-2 which suggests that sialophorin may have functional importance as a receptor for a TCR/CD3 independent T cell activation pathway.¹⁴ Reduced expression of sialophorin has also been linked to the unusually low density of surface microvilli noted on Wiskott-Aldrich lymphocytes when examined by scanning electron microscopy.¹⁵ On the basis of this finding it has been speculated that the loss of negatively charged sialic acid residues might influence the survival of lymphocytes within the circulation and accelerate the normal mechanisms of cell senescence.¹³

cDNA clones for human sialophorin have recently been obtained from T cell libraries and the derived sequence of 400 amino acids predicts a mucin-like extracellular domain (235 residues), a transmembrane region (23 residues), and a carboxyterminal intracellular domain (123 residues).¹⁶ The extracellular region contains 93 serine and threonine residues with most O-glycosylated with sialylated Gal-GalNAc units, and the intracellular domain includes a number of putative phosphorylation sites which might mediate signal transduction in an activation pathway. Since the gene for sialophorin was localised to chromosome 16, mutation events at this locus cannot be directly implicated in Wiskott-

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Aldrich syndrome.¹⁶ More probably, impaired expression of this glycoprotein is secondary to defective glycosylation. The O-linked glycans on CD43 undergo structural changes following T cell activation which might be functionally important in subsequent regulatory cell interactions.¹⁷ These changes are associated with a noticeable rise in the activity of the O-linked glycosyltransferase, B-1,6-GlcNAc transferase, and a specific deficiency of this enzyme has recently been identified in the lymphocytes of two patients with Wiskott-Aldrich syndrome.¹⁸ Although further studies are required, these observations support the view that the primary molecular lesion in the syndrome is in the biosynthesis of O-linked oligosaccharides on cell surfaces.

Bleeding tendency

The platelet defect in Wiskott-Aldrich syndrome is characterised by a reduction in cell number and mean platelet volume, abnormal ultrastructure, and impaired function. Metabolic defects and impaired aggregation responses to a range of agonists have been described.^{19,20} Reduced glycoprotein Ia and Ib expression has been reported in some instances,¹¹ but this is not a universal finding²¹ and is probably unrelated to the primary biochemical defect. Studies of platelet survival suggest that the thrombocytopenia is mainly due to increased peripheral destruction and both platelet size and number are commonly corrected after splenectomy.²²

The variable clinical expression of Wiskott-Aldrich syndrome should be emphasised because some patients may present with moderate to severe thrombocytopenia and little evidence of immune deficiency or susceptibility to infection.^{23,24} An incorrect diagnosis of idiopathic thrombocytopenia may have potentially fatal consequences, however, because these patients are highly susceptible to overwhelming sepsis if splenectomy is undertaken and the importance of long term antibiotic prophylaxis is unrecognised.^{25,26} Mild eczema is a common clinical marker and further investigation almost invariably shows small platelet size and minor abnormalities of serum immunoglobulins or deficiency of isoagglutinins. On closer examination many cases of familial X-linked thrombocytopenia probably fall into this diagnostic category and investigation of CD43 expression, lymphocyte surface morphology, and tissue specific X-inactivation analysis in carrier females (see below) might provide an additional means of identifying Wiskott-Aldrich syndrome variants in this group. Molecular genetic studies have shown that both attenuated and fully expressed forms of Wiskott-Aldrich syndrome map to similar regions of the X-chromosome short arm (Thomas N, personal communication),²⁷ which implies that different mutations of a single gene are responsible for the wide spectrum of phenotypic features.

Malignancy

Susceptibility to malignancy is well docu-

mented in patients with Wiskott-Aldrich syndrome, and in a large series reported in 1980 by Perry and coworkers² a cumulative annual risk of 2% was calculated with an overall 120-fold excess risk compared with the normal population. Most cases were of non-Hodgkin's lymphoma and extranodal presentation in the brain and gastrointestinal tract was particularly common. Perhaps surprisingly, acute myeloid leukaemia was seen in a significant proportion of the remaining cases. The development of malignancy in Wiskott-Aldrich syndrome is generally thought to be associated with decreased immune surveillance and is confined to those patients with clinically important immune deficiency. With recent therapeutic advances and improved survival, it might be anticipated that a greater proportion of patients with this complication will be encountered in the future.

Renal disease

Glomerulonephritis has recently been recognised as a relatively common complication in Wiskott-Aldrich syndrome. Patients usually present with proteinuria and haematuria, and progressive renal failure may develop.²⁴ Renal biopsies have been performed in a few patients and have shown variable histological features, including those of membrano-proliferative, mesangial, and interstitial nephritis.^{28,29} IgA nephropathy has also been noted in some patients, and immune complex deposition secondary to recurrent bronchial infections has been cited as a possible aetiological factor.³⁰ Similar renal pathology, however, has been described in families with attenuated variants and no immune deficiency.²⁸ As in the case of malignancy, progressive renal disease may be encountered more frequently in patients with Wiskott-Aldrich syndrome as their life expectancy improves.

Molecular genetics of Wiskott-Aldrich syndrome

Female carriers of Wiskott-Aldrich syndrome are phenotypically normal because there is selection against lymphoid and haemopoietic precursor cells with active X chromosomes carrying the mutant Wiskott-Aldrich syndrome gene in early embryogenesis. Consequently, until recently, genetic counselling of affected families was confined to pedigree analysis. In 1987, however, Siminovitch and Peacocke³¹ reported close linkage between the Wiskott-Aldrich syndrome gene and two loci, DXS14 and DXS7, which map to the proximal short arm of the X chromosome (p.11.3-cen). Later studies indicated that the gene is flanked by these markers and comprehensive linkage data have now been reported with a cluster of pericentromeric polymorphic markers including the closely linked hypervariable locus DXS255 and the multiallelic alpha satellite sequences identified by the probe pBamX-7 at the X centromere.^{32,33} Although the precise order of these loci in relation to the Wiskott-Aldrich syndrome gene has yet to be established, the availability of these highly inform-

active markers now allows DNA analysis to be used for carrier detection and early prenatal diagnosis in virtually all families who segregate for the disorder.

Segregation analysis using linked probes is not possible in families in which DNA from affected males is unavailable or in which only a single male is affected. An alternative strategy to identify female carriers of Wiskott-Aldrich syndrome may, however, be used. This entails analysis of the methylation patterns of X-linked genes in their lymphoid and haemopoietic cells to determine active and inactive chromosomes.^{34,35} Selective suppression of precursor cells carrying active X chromosomes with the mutant Wiskott-Aldrich syndrome gene can then be identified. Probes for the genes hypoxanthine phosphoribosyl transferase and phosphoglycerate kinase are commonly used which detect restriction fragment length polymorphisms after an initial endonuclease digestion. In heterozygous females in whom maternal and paternal alleles are identified a second digestion with a methylation sensitive endonuclease—for example, HpaII—distinguishes active loci which are cut and inactive loci which are not. It is important in such cases to confirm that the skewed X-inactivation pattern is confined to the cells expressing the defect because a small proportion of normal females (about 5%) show, by chance, an unbalanced distribution. The highly informative locus DXS255 may also be of value in X-inactivation analysis. This marker has recently been used to confirm germ line mosaicism in a Wiskott-Aldrich syndrome pedigree which failed to segregate with closely linked loci in the Xp11-q22 region.³⁶ Other groups have encountered technical problems and inconsistent results using this marker, however, and these require resolution before its full potential in such studies can be fulfilled.

Advances in management

Progress in the molecular biology of Wiskott-Aldrich syndrome has been paralleled by developments in clinical management which have made an important impact on morbidity and survival. Specific therapeutic manoeuvres include regular administration of intravenous immunoglobulin which has been shown to reduce the frequency and severity of infective sequelae, and splenectomy for selected patients who are particularly prone to serious internal bleeding. The importance of long term prophylaxis with antibiotics, with or without immunoglobulin replacement, to prevent overwhelming sepsis after splenectomy has been emphasised.³⁷ The place of HLA-matched allogeneic bone marrow transplantation as the treatment of choice is now well established and expert opinion favours early intervention if an appropriate donor is available.³⁸ Although HLA-haploidentical marrow transplants have proved less successful in Wiskott-Aldrich syndrome, mainly because of graft failure, a preliminary study suggests that this might be overcome by more aggressive conditioning regimens.³⁹ Given the pre-existing suscep-

tibility of patients with Wiskott-Aldrich syndrome to malignancy, however, it is important to determine whether such treatment leads to an unacceptably high risk of secondary tumours. An alternative approach to the problem of graft rejection has recently been advocated by Fischer *et al.*,⁴⁰ who showed that treatment of recipients with anti-LFA-1 antibody improved graft survival and outcome possibly by blockade of T cell-target cell adhesion. Finally, with accelerating developments in the molecular genetics of Wiskott-Aldrich syndrome, localisation of the mutant Wiskott-Aldrich syndrome gene is now a credible objective and retroviral mediated somatic gene transfer might offer a cure in the future.

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