The Interesting Case

Wiskott–Aldrich Syndrome—a truly interdisciplinary problem

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In this issue of Nephrology Dialysis Transplantation, Fischer and collaborators describe their problems with a patient transplanted for terminal renal failure due to IgA nephropathy with or on the basis of the Wiskott–Aldrich syndrome (WAS) [1,2]. This syndrome is hardly familiar to most nephrologists. We therefore illustrate the signs, symptoms, the findings and problems of a patient and his family burdened with this inherited disease.

Case report

In 1983 this patient presented as a 29-year-old man with a past history characterized by repeated bouts of acute otitis media, repeated episodes of bronchitis, conjunctivitis, cutaneous abscesses, and various minor local infections. A massive herpes zoster ophthalmicus during childhood required treatment with hyperimmune serum. Starting in early childhood the patient suffered from eczematoid skin changes of atopic distribution (legs, upper thorax, fingers) and petechial lesions, suffusions, repeated nose bleedings, an episode of macrohaematuria and chronic microhaematuria.

The following rather constant laboratory findings accumulated in the years prior to 1979: haemoglobin 151 g/l with reticulocytes around 5%; a normal leucocyte count with eosinophils of 265 × 10⁶/l, a lymphopenia of 1.5 × 10⁹/l and a platelet count of 10 × 10⁹/l (normal morphology). In 1979 the patient underwent splenectomy for a traumatic splenic rupture, following which the platelet count was consistently above 100 × 10⁹/l, and purpura, bleedings and macrohaematuria disappeared.

It turned out early in the patients history, that he is a member of the fifth known generation of a vast family, studied at the Zurich childrens hospital in 1975 for similar problems (Fig. 1): at that time 8 (by now 10) of the male members of the fourth and fifth generation of the kinship had died in early childhood, a further seven affected males suffered from similar manifestations of WAS (Fig. 2) and seven were female carriers.

In 1983 the patient underwent work-up for arterial hypertension. The laboratory findings revealed a creatinine of 210 μmol/l (2.37 mg/dl), a creatinine clearance of 49 ml/min and a serum protein of 63 g/l; proteinuria 4.2 g/d, microhaematuria and red cell casts. Renal biopsy showed a membranoproliferative IgA nephritis with focal and segmental accentuation and crescents in 4/17 glomeruli (Figs. 3 and 4). By 1985 the patient was in terminal renal failure and—based on his own
The patient and his family show all the characteristics of WAS—thrombocytopenia with platelets reduced in size and function; eczema of atopic distribution and defects in cell-mediated immunity and antibody response to carbohydrate and other antigens.
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Fig. 4. Renal biopsy of the propositus. Immunohistochemistry for IgA.

Accordingly the main clinical manifestations are purpura, suffusions and bleedings; chronic eczematoid skin changes, and chronic infections. The syndrome is inherited in an X-linked manner, females acting as carriers. Recently the mutated gene has been identified and cloned [3].

WAS patients lack a cell-surface molecule, sialophorin (CD43), a ligand for the adhesion molecule ICAM-1 [3–5]. Sialophorin is involved in T-cell proliferation and apparently necessary for normal lymphocyte, platelet and monocyte function. T-cell immunity may be normal initially, but immunodeficiency tends to progress with time, resulting in a reduction in T-cell number and function. In parallel with the typically absent antibody response to pneumococcal polysaccharide antigens the early infections turn out to be mainly due to Streptococcus pneumoniae and Haemophilus influenzae. With progression of the immune deficiency viral and protozoan infections may also occur.

While in infancy many of the patients die with massive bleeding episodes, older children succumb to overwhelming infections—often of the upper respiratory tract. Malignancy (mainly malignant lymphoma) is an accepted risk in the young adult patient. Less well known, but meanwhile a repeatedly confirmed complication of WAS in later life is a chronic progressive nephropathy of the IgA type [7–11]. The pathogenesis of IgA nephritis, particularly in WAS, is not well understood. Whether it is simply a consequence of recurrent infections, chronically increased serum IgA levels and circulating IgA antigen-antibody complexes [10] or associated with the chronic platelet disorder [11] remains to be seen.

This family then exhibits the whole spectrum of the Wiskott–Aldrich syndrome and the two brothers reported in this issue of Nephrology Dialysis Transplantation share most of its early and late complications up to IgA nephropathy and malignant lymphoma.

References

2. Aldrich RA, Steinberg AG, Campbell DC. Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics 1954; 13: 133–139

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