PART XV

PAEDIATRIC NEPHROLOGY

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R K A Kluthe
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HEREDITARY GLOMERULONEPHRITIS OF NON-ALPORT TYPE

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Summary

In three unrelated kindreds, 21 subjects with hereditary renal disease were identified. The mode of inheritance was autosomal dominant and the main clinical features were asymptomatic proteinuria and/or haematuria. Three of the 16 females but none of the five males developed progressive renal failure. Renal biopsy carried out in six of the 21 patients showed varying degrees of mesangial change with glomerular deposition of IgM and C3 in some cases. Nerve deafness and renal ultrastructural changes typical of Alport’s Syndrome were absent. The renal disease in these subjects does not conform with previously recognised types of familial nephropathy.

Introduction

The term hereditary nephritis encompasses a number of different conditions. Alport’s Syndrome [1] is a progressive nephritis predominantly affecting males in association with nerve deafness and a characteristic ultrastructural lesion of the glomerular basement membrane (GBM). Benign familial haematuria [2] is distinguished by its non-progressive nature and the differing ultrastructural appearances of the GBM. A number of other less common forms of hereditary nephritis are also recognised [3].

This study reports three kindreds with hereditary nephritis which does not conform with these previously described types of familial nephropathy.

Patients and methods

The occurrence of chronic renal failure (CRF) in two sisters and their mother prompted a study of other family members, and subsequently of two unrelated kindreds also with hereditary renal disease. Forty-three subjects were examined comprising nine males and thirty-four females ranging in age from five to 58 years.
Figure 1. Pedigrees of the three families. For details of patients 1–21, and a–e, see text
Microscopic haematuria was defined as more than five red blood cells per high power field, and significant proteinuria as twenty-four hour urine protein in excess of 300mg in males, 500mg in females. Non-proband subjects were considered to be affected if they had persistent proteinuria or microhaematuria or both. The conclusion that death occurred due to renal failure in three ascendants (Figure 1) was based on information from relatives but these subjects are not included in the total number of cases identified. Investigations included chromatography of urinary amino acids (10 patients), measurement of C₃ and C₄ complement (17 patients), peripheral blood film examination (9 patients) and audiometry (14 patients). Renal specimens, five biopsy and two nephrectomy, were examined. Tissue for light microscopy was fixed in 10 per cent mercuric formol and embedded in paraffin wax. Sections were stained by H and E, PAS, silver and trichrome methods. Snap frozen tissue was prepared for immunofluorescence using Behring antisera. For electron microscopy, small tissue cubes were fixed in buffered glutaraldehyde and embedded in an epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate.

Results

Clinical data

In Family 1, there were four patients. Fourteen other relatives were studied but none had renal disease. Patient 1 presented with hypertension, proteinuria of 6.5g/24 hour and CRF (creatinine clearance 44ml/min) at age 26. She commenced regular dialysis therapy (RDT) at age 28, and received a renal transplant (RT) at age 30 which continues to function well six years later. Her mother (Patient 2) presented at age 50 years with hypertension, proteinuria 2.8g/24 hour and CRF. She commenced RDT at age 53 years, received a RT at 56 years but died from metastatic breast carcinoma within a year. Her sister (Patient 3) had asymptomatic proteinuria (4.3g/24 hour) at age 20, developed CRF with hypertension by age 32 and progressed to RDT within two years. Her maternal uncle (Patient 4) had asymptomatic proteinuria (1.7g/24 hour) at age 46 and did not develop hypertension or impaired renal function over ten years of subsequent follow-up. Her maternal grandfather (not seen, Patient a) was said to have died aged 50 years from hypertension and ‘kidney trouble’.

In Family 2, three affected patients were attending the Renal Unit. Patient 5 had ankle swelling from age 17 and was found to have a mild nephrotic syndrome on investigation at age 29. She remains normotensive and without impairment of renal function seven years later. The father of Patient 5 (not seen, Patient b) and one paternal uncle (not seen, Patient d) had hypertension and ‘protein in the urine’; her paternal aunt (not seen, Patient c) died from ‘kidney failure’ at age 21 years. Patient 6 presented with a severe nephrotic syndrome at age eight and this persists eight years later. Patient 7 was found at age 20 to have hypertension and nephrotic syndrome which persists six years later. Thirteen other members of this kindred were studied and seven had renal disease (five females, two males, ages three to 49 years). Two had detectable oedema
and two mild hypertension. Six of the seven had micro-haematuria, associated in four of the six with proteinuria. One patient had isolated proteinuria. None of the seven patients had impaired renal function.

In the third family, two patients were attending the Renal Unit. Patient 8 had asymptomatic proteinuria and haematuria during her first pregnancy at age 25 and this persists eight years later. Her mother (not seen, patient c) was said to have had similar urine abnormalities during pregnancy but had never been further investigated, and is alive and well aged 60 years. Patient 9 presented with recurrent haematuria at age three years. Study of eight other members of this kindred showed a further five had renal disease (four female, one male, age range three to 34 years) manifested in three by micro-haematuria and in two by proteinuria and haematuria. None of the five had impaired renal function.

Ancillary investigations

No patients showed any abnormality on urine amino acid chromatography, measurement of serum complement and immunoglobulins, or peripheral blood examination. Audiometric testing showed a unilateral mild high tone loss in Patient 1, mild conductive loss due to chronic secretory otitis media in Patients 6 and 14, and an unusual ‘flat’ hearing loss of mild degree over all frequencies in Patient 3.

Morphological study

Patient 1 (bilateral nephrectomy) showed advanced glomerular sclerosis, mesangial hypercellularity and interstitial fibrosis with hypertensive vascular changes. Patient 3 (biopsy at age 32 years) showed no significant glomerular changes on light microscopy (LM). Three of seven glomeruli studied by immunofluorescence (IF) contained peripheral deposits of C3 and one contained a peripheral deposit of IgM. Bilateral nephrectomy at age 34 showed glomerular sclerosis, mesangial hypercellularity and hypertensive vascular changes. IF demonstrated C3 and IgM in glomeruli. Patient 4 (biopsy at age 46 years) showed segmental mesangial matrix increase with trichrome positive deposits. There was peripheral glomerular C3 deposition on IF but no immunoglobulins were detected. There was regular widening of the glomerular basement membranes (GBM) — not fibrillar — on electron microscopy (EM). Patient 5 (biopsy at age 29 years) had widespread foam cells. IF showed a little mesangial IgA deposition and on EM the GBM was even in width and not fibrillated. There were a few small electron-dense mesangial deposits. Patient 6 (biopsy age 13 years) showed mesangial proliferative glomerulonephritis and foam cells. IF revealed mesangial and capillary wall deposits of IgM and C3. On EM the GBM appeared even but there were a few foci of irregularity. Patient 8 (biopsy age 26 years) had very mild diffuse mesangial hypercellularity. IgM was present at the periphery of one glomerulus and on EM the GBM was generally normal apart from a few small foci of irregularity with lamination (Figure 2).
Figure 2. Patient 8
(a) Upper: Two adjacent capillary walls. Foot process fusion. No GBM lesion.
(b) Lower: Capillary wall from another glomerulus. Foot processes intact. Small foci of GBM lamination.
Uranyl acetate and lead citrate × 5400, × 6000
Discussion

Three kindreds are described in this study which is a preliminary report of a wider investigation, including histocompatibility typing.

Family 1 is characterised by a female preponderance with CRF occurring in two sisters in early adult life and in their mother at an older age (50 years). Although the pathological findings in these sisters indicate end-stage glomerulonephritis of mesangial proliferative type, there is renal disease in their relatives. It is not yet certain if the glomerular abnormalities in the maternal uncle are comparable with those in the other family members.

Family 2 again has a female preponderance. On light microscopy foam cells were a prominent feature in the two biopsies but these are not specific for hereditary nephritis [4]. In Patient 6 there were some focal glomerular basement membrane changes reminiscent of Alport’s Syndrome but these changes were not widespread and were not seen in Patient 5. Other features of Alport’s Syndrome such as nerve deafness were not seen in these patients or their affected relatives. The index patient in Family 3 (Patient 8) had mild mesangial proliferative glomerulonephritis with very focal basement membrane lamination. Consent for biopsy of the younger male relatives with urinary abnormalities has not so far been granted.

The renal lesion in these three families differs from previously recognised forms of familial glomerulonephritis [3], and further investigation will be necessary to define more precisely the nature of the pathological lesion. While no definite link has been demonstrated among the three kindreds, it is possible that some inherited defect of mesangial function may play an important role. The study also suggests that in patients with mesangial proliferative glomerulonephritis a search for other affected relatives should be considered.

Acknowledgments

The authors thank Mr J Byrne, Consultant ENT Surgeon, Belfast City Hospital, the Renal Unit nursing staff, the technical staff of the Department of Pathology, Miss Karen Gilmore and Miss Linda Cairns for secretarial assistance and Mrs P Clark for final typing.

This investigation was supported by the Northern Ireland Kidney Research Fund.

References

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Open Discussion

BONE (Liverpool) Nerve deafness is often a late manifestation in Alport's Syndrome. If these patients developed deafness would you be tempted to use the term Alport's Syndrome to describe their condition?

DOHERTY It is true that deafness is not a universal feature of Alport's Syndrome. However, in addition to the absence of deafness, these subjects had none of the typical glomerular basement membrane changes seen in Alport's Syndrome, and there appeared to be a female rather than a male predominance. These three features make me unwilling to call them Alport's Syndrome. I think the diagnosis of Alport's Syndrome should be reserved for unequivocal cases, otherwise we run a risk of creating confusion.

KNAPP (Nottingham) We have a kindred, which has many similarities of which there are over 100 members. The main difference is that ours do have a male predominance in those patients with progressive renal failure of whom there are several. We have performed HLA and DR typing on all of the kindred and though I am hesitant to give information on the statistical analysis of the situation which is not yet finalised, our impression is that there is a definite linkage with certain DR loci and I wondered if you have any analysis of this sort and whether you thought it might be another method of classifying this heterogeneous group of people?

DOHERTY HLA and DR typing of these subjects has been carried out but the data is as yet incomplete and it would be premature for me to comment on it. Perhaps I might say that results available so far, although incomplete indicate that in two of the families, HLA A2 is present in those with nephritis and not in those without nephritis. HLA A2 is however a common antigen present in about 50 per cent of the population. I have not yet had the opportunity to analyse the data on DR typing.

RITZ (Heidelberg) I would concur with your conclusion that non-immune mediated familial glomerulonephritis may not necessarily show the typical ultrastructural changes of Alport's disease. Dr Waldherr from Heidelberg will report next week to the German Society of Nephrology exactly similar findings which are in support of your observations and conclusions.