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Autosomal Recessive Early-Onset Nephropathy with Progressive Focal Glomerulosclerosis

Key Words

Autosomal recessive
Arab
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Abstract

We report an inbred Arab family from Oman with 5 children affected with an early-onset nephropathy and an early progression to renal failure. All patients presented with eyelid swelling, proteinuria and microscopic haematuria associated with growth failure. The patients did not present gross oedema or clinical nephrotic syndrome in spite of massive proteinuria and hypoproteinaemia, and there was no response to steroid. Renal biopsy showed progressive focal glomerulosclerosis in 2 of them and an unusual appearance in the 3rd child with deposition of electron-dense immune complexes in the mesangium and subendothelial position. It may be that this is a new type of nephropathy leading to focal glomerulosclerosis. Mapping the gene for this type of nephrosis should be possible in this family using the concept of homozygosity mapping.

Introduction

Nephropathy with onset in infancy is not common [1, 2]. Classifications have been proposed according to aetiology, histopathological changes, response to therapy, prognosis and mode of inheritance [1–3]. We report a consanguineous Arab family from Oman with 5 children affected with an early-onset ne-

phropathy characterized by its early onset, resistance to steroid and progression to end-stage renal failure in childhood. Renal biopsy showed unusual findings in 1 child and focal glomerulosclerosis in the other 2 children, indicating that the glomerulosclerosis is perhaps the end result rather than the primary cause of their nephropathy.

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Fig. 1. The pedigree of the family.

The Family

The family is multiply consanguineous of Omani origin. There are a total of 8 children in two sibships, 5 of whom are affected (fig. 1). Urine analysis on the normal children and the parents showed no abnormalities. One affected child (III₁) died of renal failure at the age of 2.5 years.

Case 1 (III₃)

A 10-year-old female child, product of normal pregnancy and delivery with a birth weight of 2.5 kg, was examined. She was first evaluated in our department at the age of 6 years because of a history of intermittent periorbital oedema with proteinuria and microscopic haematuria since the age of 2 years.

Examination at 6 years revealed a weight of 12.5 kg and height of 103 cm (both below 3%), puffiness of eyelids and normal blood pressure. There were no dysmorphic features and her developmental milestones were normal for her age.

Urine examination revealed 3+ protein and 40 RBCs per high power field (HPF) and granular casts. A 24-hour urinary protein estimation was 23.3 mg/kg/h. Serum creatinine was 23 pmol/l units, and creatinine clearance ranged from 47.5 to 53.2 ml/min/1.73 m². Total serum protein was 49 g/l with serum albumin of 7 g/l. Serum cholesterol was 10.6 mmol/l with normal

serum triglycerides. Serum urea electrolytes and creatinine were within normal limits. Her haemoglobin was 10.7 g % and peripheral blood smear showed hypochromia and microcytosis. Renal ultrasound and intravenous pyelography showed large kidneys on both sides with duplication of the right pelvis. Evaluation for hepatitis B was negative.

She was started on a course of corticosteroid but her condition deteriorated with massive accumulation of fluid in the trunk and genitalia, sparing the extremities totally. Her weight increased by 5 kg (17.5 kg) within 2 weeks.

Due to massive oedema which had immobilized the patient, indomethacin was initiated and corticosteroids were suspended. This resulted in amelioration of the oedema and improvement in the general condition of the patient. However, renal function as evaluated by creatinine clearance did not show any change. She is now 10 years old with end-stage renal failure and is on dialysis.

Renal biopsy at 6 years of age revealed 15 glomeruli on light microscopy. They were enlarged and slightly lobular. Three glomeruli showed adhesions of the tuft to Bowman's capsule, associated with local collapse of the tuft and a little fibrin deposit (fig. 2). There was one hyalinized glomerulus. Tubules were well preserved and there were no interstitial fibrosis or vascular changes. Immune histology showed non-specific occasional deposits of IgG and IgM. Electron microscopy showed widespread foot process fusion and extensive microvillous transformation, vacuolation of podocytes, compatible with massive proteinuria.

Repeat biopsy at 10 years of age showed considerable deterioration in renal pathology with significant

Fig. 2. Case 1. A glomerulus ($\times 200$) stained with haematoxylin and eosin (HE) showing a little periglomerular fibrosis, several adhesions of the tuft to Bowman's capsule, and sclerosis of the middle part of the tuft, with more normal capillary loops at the periphery.

tubular and glomerular loss. Immunofluorescent examination revealed focal and segmental deposition of IgM (grade 3), IgA (grade 1) within glomeruli, C₃ and C₄ in hypertrophied tubules, and C₃ in some blood vessels. There was also fibrin deposition in the interstitium and interstitial capillaries. These findings were consistent with advanced focal glomerulosclerosis.

Case 2 (III₆)

A 1-year-old female child, sister of case 1, presented with puffiness around the eyes since the age of 6 months. Physical examination revealed a weight and height below 3%, normal blood pressure and slight oedema of eyelids with no other abnormalities. Urine analysis showed 3+ proteins and 72 RBCs/HPF with some granular casts. Total serum protein was 28 g/l with serum albumin of 10 g/l; 24-hours urine for protein was 15 mg/kg/h. Serum urea electrolyte and creatinine were normal. Intravenous pyelography showed normal kidney, ureters and bladder. Evaluation for hepatitis B infection was negative.

After starting her on a course of corticosteroids (prednisolone) she accumulated massive trunk oedema and ascites with associated increase in weight from 6 to 7.5 kg in 6 days. Prednisolone was then discontinued. A course of indomethacin was started which resulted in rapid improvement in the child's condition within a period of 4 days, as judged by the disappearance of oedema and improvement in the general condition of the patient. She has maintained a fairly acceptable renal function with decrease in creatinine clearance of

10 ml/min/1.73 m². Renal biopsy at 1 year of age showed 21 glomeruli on light microscopy, of which one showed global sclerosis. The remaining glomeruli appeared moderately enlarged with mild attenuation of the matrix with capsular adhesion at several sites (fig. 3, 4). Tubules were well preserved and showed extensive hyaline droplets. Arteries appeared normal and there were no fibrosis scarring and amyloid deposition. Immune histology showed traces of IgG in three glomeruli which also contained significant deposits of IgM in the mesangium and capillary loops. Electron microscopy showed widespread foot process fusion associated with microvillous changes in the podocytes and normal basement membrane.

Case 3 (IV₂)

A male infant of 11 months of age presented with a history of intermittent puffy face since the age of 6 months. An examination revealed a thin wasted looking child with distended abdomen (weight and height <3%) and puffy eyelids. Other abnormalities were not detected and his developmental milestones were normal for his age.

Urine analysis showed 3+ protein and 10 RBCs/HPF with 2+ granular casts. Serum protein was 42 g/l and serum albumin 3 g/l, cholesterol was 7.29 mmol/l (normal range 3.1–5.6 mmol/l). The rest of his blood chemistry was normal. Evaluation for hepatitis B was negative. An ultrasound of the kidneys showed large kidneys on both sides with a low position of the right. Progression of his illness has been more severe than case 2

Fig. 3. Case 2. A glomerulus ($\times 200$) stained with periodic acid silver methenamine (PASM). The glomerulus is moderately enlarged and shows a diffuse increase in mesangial matrix, with some increase in mesangial cells.

Fig. 4. Case 2. A glomerulus ($\times 200$) stained with HE which is slightly enlarged and shows a mild increase in mesangial cellularity with possible capsular adhesions at several sites.

and is now in the third stage of renal failure with decrease in creatinine clearance of 30 ml/min/1.73 m².

Renal biopsy at 11 months of age on light microscopy revealed 10 glomeruli of which one showed global sclerosis and the remaining were enlarged, lobular, and had mild mesangial hypercellularity (fig. 5). Occasional capsular adhesion was seen (fig. 6). Beneath the capsule of the kidney there was an interstitial infiltrate of lymphocyte and the occasional plasma cells. Tubules were generally well preserved but there were at least two small foci of early atrophy (fig. 7). On immunofluorescence staining there were mild granular deposits of IgG and IgM in the mesangium and on some of the basement membrane. Electron microscopy revealed excessive foot process fusion and numerous microvilli.

There were dense (immune) deposits in the mesangium and subendothelial position, and increase in mesangial cells and matrix.

Case 4 (III₅)

A 4-year-old male child (brother of cases 1 and 2) presented with intermittent periorbital oedema. There were no other complaints. An examination revealed puffy eyelids. Urine examination revealed 3+ proteinuria and 2+ blood with occasional granular casts. His blood pressure was normal for his age. Parents refused kidney biopsy and further renal evaluation.

Fig. 5. Case 3. A glomerulus ($\times 400$) stained with PASM. The glomerular basement membranes are of normal thickness. There is a moderate increase in mesangial matrix.

Fig. 6. Case 3. A glomerulus ($\times 400$) stained with HE showing an area of focal mesangial hypercellularity with adhesion to Bowman's capsule.

Fig. 7. Case 3. A glomerulus ($\times 200$) stained with PASM. There is tubular atrophy surrounding the glomerulus and a marked increase in the mesangial matrix to form a nodule in which a considerable number of mesangial cells are seen.

Discussion

The nephrosis in this family is characterized by its early onset, progressive focal glomerulosclerosis and rapid progression to renal failure.

The multiple consanguinity in the family and the presence of several affected children of both sexes with normal parents indicate autosomal recessive inheritance. Focal glomerulosclerosis can be defined as sclerosing glomerulopathy in which some glomeruli are involved at least initially and in which the sclerosing lesions generally affect a part of the glomerulus [4]. The disease may be in the primary or secondary stage occurring as a complication of other diseases, renal or non-renal, and could occur as an isolated entity or as a part of a well-defined malformation syndrome. Examples of recessive syndromes associated with nephropathy include Hutterite cerebro-osteo-nephrodysplasia syndrome [5], Galloway-Mowat syndrome of microcephaly, abnormal gyral pattern, developmental retardation and glomerulopathy [6], and the syndrome of microcephaly, marfanoid habitus and focal segmental glomerulopathy [7].

Familial cases of non-syndromic glomerulosclerosis presenting with nephrotic syndrome showing autosomal recessive mode of inheritance have also been reported. Naruse et al. [8] reported two sibs of consanguineous parents with nephrotic syndrome which developed at the age of 14 and 15 years. In both the disorder was resistant to steroid. Renal biopsy in 1 of them was typical of focal glomerulosclerosis.

Schwarz et al. [9] reported 3 sibs with focal glomerulosclerosis. Tejani et al. [10] reported 3 unrelated hispanic families with more than 1 individual affected with nephrotic syndrome. The histological lesion in the children was either focal segmental glomerulosclerosis, or IgM nephropathy evolving into focal scler-

osis. Similarly McCurdy et al. [11] reported on 3 siblings of a single hispanic family with early-onset nephrosis. Renal biopsy revealed focal segmental glomerulosclerosis and mild diffuse mesangial hypercellularity.

All the children in this report had evidence of nephropathy very early in their lives including symptoms like eyelid swelling, proteinuria and microscopic haematuria in addition to stunted growth. There were no dysmorphic features however, to suggest any of the known syndromes associated with early-onset nephropathy. In addition, the clinical and pathological features as well as the response to treatment in the sibs in this report are different from other reported cases of focal glomerulosclerosis. For example, the disorder started at an early age in this family (documented in the 1st year of life in 2 of them), and in spite of massive proteinuria and hypoproteinemia no gross oedema and clinical nephrotic syndrome were observed at any time. Therapy with corticosteroid resulted in massive accumulation of fluid in the trunk (more than 10% of body weight) within 3–4 days, and the extremities were totally spared. This phenomenon recurred when the patient was rechallenged with corticosteroid in another institution.

Several periodic renal biopsies as well as an early biopsy at 11 months of age threw some light on the possible sequence of events of the pathology of the kidney at different ages in this family. For example, in the first case there was clear evidence of focal glomerulosclerosis at 6 years of age which progressed significantly by 10 years of age. The second case had findings of early glomerulosclerosis at 1 year of age while renal biopsy in the third case at 11 months of age showed no evidence of focal glomerulosclerosis. There were interstitial infiltrate of lymphocyte and plasma cells beneath the capsule, foci of tubular atrophy and marked increase in the mesangial matrix and

mesangial cells. In addition there were electron-dense (immune) deposits in the mesangium and subendothelial position on electron microscopy. The presence of these complexes at an early age could indicate an immunological process starting early in infancy or even perhaps from birth, gradually affecting the glomeruli and resulting in renal damage and sclerosis. The observation of progression of focal glomerulosclerosis from very early to advanced stage of development suggests that the glomerulosclerosis is the end result of the nephropathy in this family rather than the primary cause.

Recently, using whole genomic linkage analysis in 9 multiple families of European or

North African origin the gene for idiopathic autosomal recessive nephrosis was localized to 1q25–1q31. However, genetic heterogeneity was also suggested since linkage in one family was negative [12].

In view of the large pedigree size and multiple consanguinity in this family, mapping of the mutant gene by linkage analysis and identity by descent should be possible.

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References

- 1 Grislain JR, Mainard R, Berranger P, Cacludal JL, Pinel J: Le syndrome néphrotique au cours de la première année de la vie. *Ann Paediatr* 1973;20:120–137.
- 2 George CR, Hickman RO, Stricker GE: Infantile nephrotic syndrome. *Clin Nephrol* 1976;5:20–24.
- 3 Kaplan BS, Bureau MA, Drummond KN: The nephrotic syndrome in the first year of life: Is a pathologic classification possible? *J Pediatr* 1974;85:615–621.
- 4 Magil A: Focal and segmental glomerulosclerosis. *Mod Pathol* 1991;4:383–391.
- 5 Opitz JM, Lawry RB, Holmes TM, Morgan K: Hutterite cerebro-osteonephrodysplasia: Autosomal recessive trait in a Lehrerleut Hutterite family from Montana. *Am J Med Genet* 1985;22:521–529.
- 6 Galloway WH, Mowat AP: Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. *J Med Genet* 1968;5:314–321.
- 7 Houlston RS, Iraggori S, Murday V, Scrine M, MacDermot K, Slack J, Rees L: Microcephaly, focal segmental glomerulonephritis and marfanoid habitus in two sibs. *Clin Dysmorphol* 1992;1:111–113.
- 8 Naruse T, Hirokawa N, Maekawa T, Azato T, Ito K, Kaya H: Familial nephrotic syndrome with focal glomerular sclerosis. *Am J Med Sci* 1980;280:109–113.
- 9 Schwarz R, Stoegmann W, Fischbach H: Familiäres nephritisches Syndrom mit Glomerulosklerose. *Wien Klin Wochenschr* 1976;88:548–554.
- 10 Tejani A, Nicastrì A, Phadke K, Sen D, Adamson O, Dunn I, Calderon P: Familial focal segmental glomerulosclerosis. *Int J Pediatr Nephrol* 1983;4:231–234.
- 11 McCurdy F, Butera P, Wilson R: The familial occurrence of focal segmental glomerular sclerosis. *Am J Kidney Dis* 1987;6:467–469.
- 12 Fuchshuber A, Jean G, Gribouval O, Gubler M, Broyer M, Beckmann J, Niaudet P, Antignac C: Mapping a gene (SRNI) to chromosome to 1q25–1q31 in idiopathic nephrotic syndrome confirms a distinct entity of autosomal recessive nephrosis. *Hum Mol Genet* 1995;4:2155–2158.