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FAMILIAL FOCAL SEGMENTAL GLOMERULOSCLEROSIS IN INFANCY*

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In 1901 Atlee described various forms of familial nephropathies. However, the most common form is Alport's syndrome. Familial nephrotic syndromes are found with less frequency, and constitute a heterogenous entity as to clinical and hereditary findings and renal histopathology[1].

In 1951, Fanconi defined the familial nephrotic syndrome of childhood as characterized by the occurrence of the disease in multiple siblings and onset after infancy[2]. Other investigators have suggested that the familial nephrotic syndrome should be distinguished from the Finnish type congenital nephrotic syndrome by the age at onset, and from the sporadic nephrotic syndrome by its increased severity, poorer response to therapy and worse prognosis[1-3].

A recent survey of European children showed that 4-6% of the nephrotic children had a familial nephrotic syndrome involving sibling pairs (Table I). The familial incidence of the nephrotic syndrome is virtually confined to siblings with only one well-documented instance of involvement in more than one generation[2]. The inheritance appears to be polygenic, and environmental as well as genetic factors are involved in the etiology of the nephrotic syndrome[2].

We report two siblings who developed steroid-resistant nephrotic syndrome. The renal biopsy specimen obtained from one patient showed typical findings of focal glomerulosclerosis.

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TABLE I: Review of the Literature

1901	Atlee	Familial nephropathies
1951	Fanconi	Familial nephrotic syndrome
1969	Norio et al	11 Pairs of concordant monozygotic twins
		16 Affected sibling pairs
		11 Nephrotic patients with close relatives
1971	Roy and Pitcock	12 Pairs of affected monozygotic twins
		8 Cases with NS in 3 families - 3 FGS - 5 INS
1973	Habib et al	6 Infant monozygotic twins - 6 DMS
1974	Bader et al	16 Familial NS in 70 patients with INS
		- 1 Pair of monozygotic twins
		- 5 Affected sibling pairs FGS
		- 2 Affected first cousins
1980	Naruse et al	2 Brothers with NS - 2 FGS
1981	Chandra et al	3 Siblings with NS - 3 FGS
1983	Yoshikatsu et al	2 Monozygotic twins - 2 DMS
1985	Sanchez et al	3 Generations in a family - 6 FGS

NS : Nephrotic syndrome
INS : Idiopathic nephrotic syndrome
FGS : Focal glomerulosclerosis
DMS : Diffuse mesangial sclerosis

Case Reports

Case 1

A fifteen-month-old girl was admitted to the Hacettepe University Children's Hospital presenting with edema on the face and proteinuria on routine examination. Her parents were first cousins and she had no family history of previous renal disease. On admission her blood pressure was 100/60 mm Hg, body weight 8.500 g and height 79 cm. She had skin pallor and periorbital edema was observed. The infant, who was severly ill, presented with signs of dehydration. Laboratory findings revealed hemoglobin 9.95 g/dl; White Blood Cell count 3200/mm^3. Urinalysis showed proteinuria (++) with 8-10 leukocytes and a few red blood cells. Serum electrolyte levels were within normal limits. Total serum protein was 3.8 g/dl, albumin 1.5 g/dl, total cholesterol 162 mg/dl, and total lipids 630 mg/dl. *Escherichia coli* was detected in the urine culture. Despite antibiotic therapy, the patient's general condition deteriorated and she died of septicemia on the second day of therapy.

Case 2

The one-year-old brother of Case 1 who had developed periorbital edema was admitted to the Hacettepe University Children's Hospital two years after his sibling's admittance. On physical examination the blood pressure was 150/110 Hg, body weight 9.300 g, and height 73 cm. Generalized edema was noted. Laboratory findings revealed hemoglobin 9 g/dl; White Blood Cell count 21.200/mm^3. Random urinalysis showed proteinuria (++++), granular casts, and 3-4 red blood cells. The protein-creatinine ratio was 35. Total serum protein was 3.5 g/dl, albumin 1.6 g/dl, total lipids 1600 mg/dl, total cholesterol 4600 mg/dl, BUN 11 mg/dl, creatinine 0.6 mg/dl, uric acid 9.1 mg/dl, C_3 120 mg/dl, and C_4 60 mg/dl. Serum electrolytes were within normal limits. An excretory urogram revealed enlarged kidneys.

The patient was treated with prednisolone 60 mg/m^2 body surface daily for four weeks, however the treatments proved to be ineffectual. The child was then given cyclophosphamide therapy. Since he again failed to respond to the therapy, a renal biopsy was performed.

Five of 21 glomeruli showed focal segmental sclerosis in the renal biopsy specimen. Tubular atrophy and arteriolar thickening were observed in some areas (Figs 1,2). Immunofluorescent study disclosed negative staining with IgG, IgA,

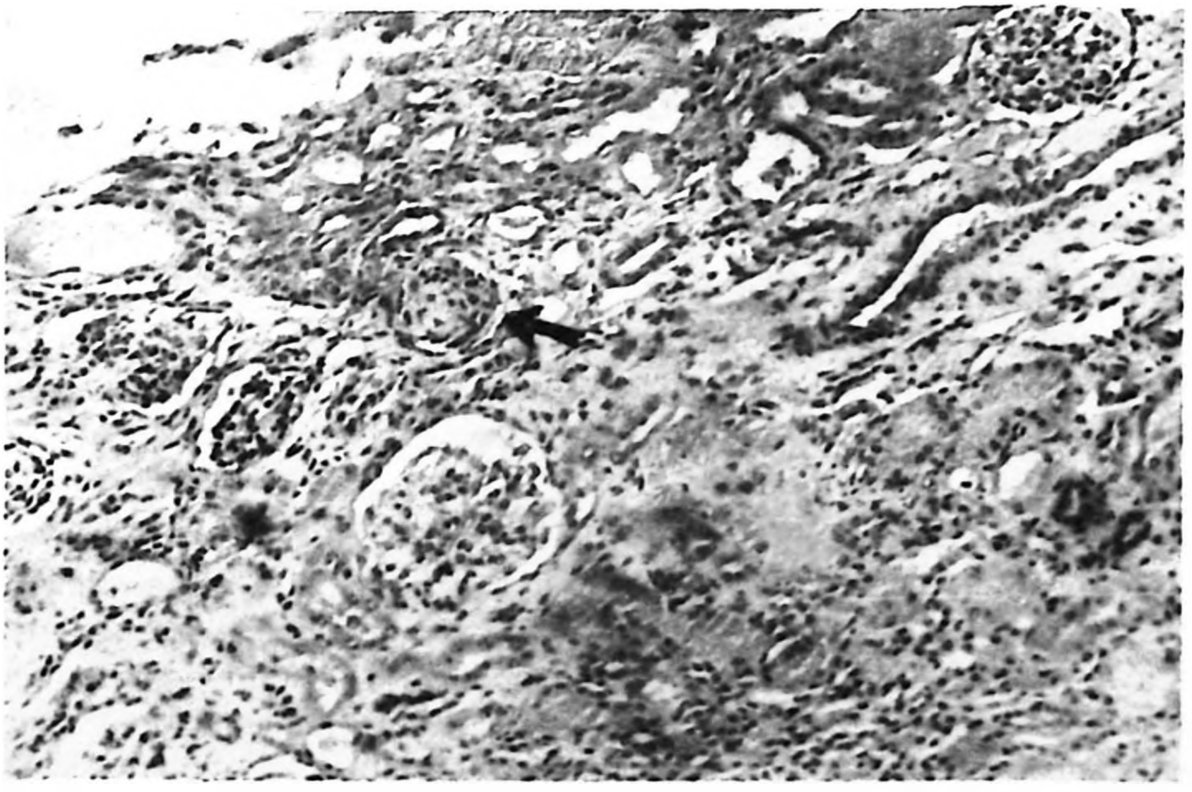

Fig. 1: Under lower magnification the glomeruli are varied in size. One small glomerulus (arrow) shows a large area of glomerulosclerosis in the tuft. Note the tubular atrophy present in this section (H and E stain).

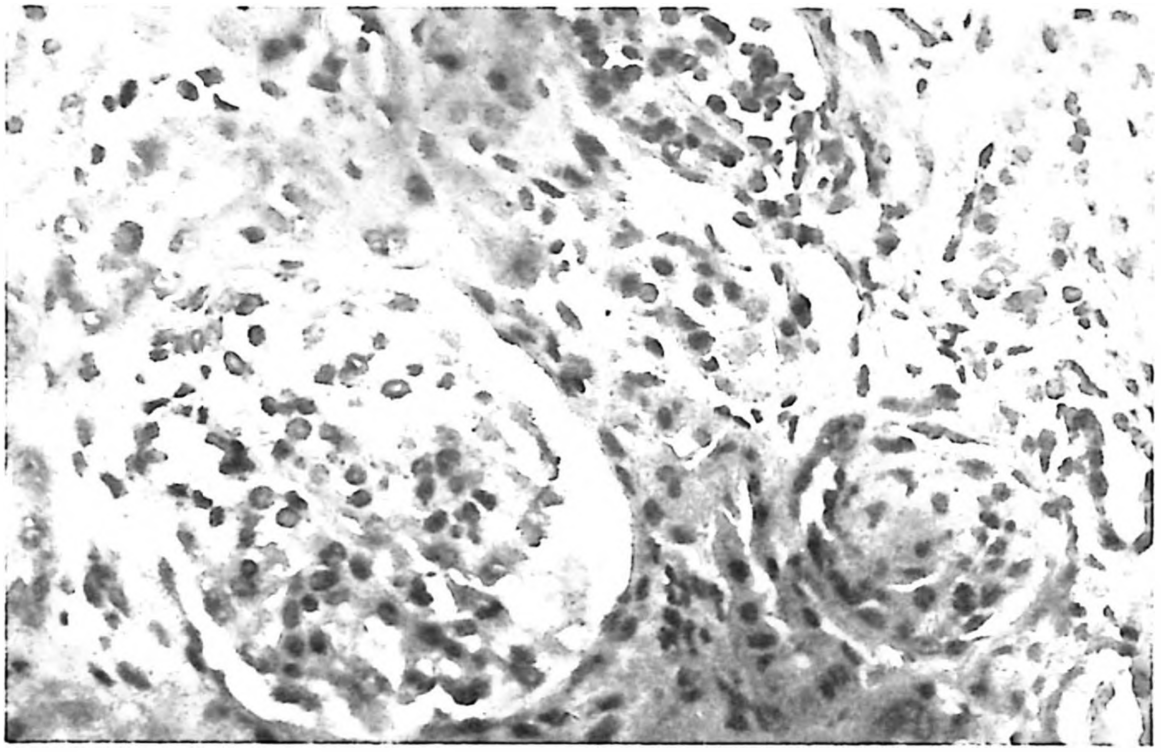

Fig. 2: Under higher magnification of the area seen in Fig. 1, normal appearing and sclerosed glomeruli are present (H and E stain).

IgM, C_3, C_{1q}, and fibrinogen. The biopsy diagnosis was focal segmental glomerulosclerosis (FSGS). Treatments with chlorambucil and dipyridamole were started, however no response was obtained. Three months later the patient died due to pyocyaneus sepsis.

Discussion

Familial incidence of the idiopathic nephrotic syndrome (NS) has been previously stressed, and its occurrence in the siblings of patients with NS is reported to be 1000 times greater than in the general population[2]. This greatly increased incidence in siblings suggests that genetic factors may play a major role in this disease.

Morphologically, focal glomerulosclerosis is observed in most of the familial cases[4-9]. Tejani et al[9] noted the dominance of the HLA DRW8 antigen in his cases of FSGS and postulated that there is a genetic tendency for this type of nephropathy to develop in patients with this particular tissue type. The reported cases in the offspring of consanguineous marriages favor an autosomal recessive inheritance pattern. This may be particularly important in our country since the rate of consanguinity is quite high. New cases might serve to enlighten this etiologic aspect[10,11]. On the other hand, Tomero et al[8] reported FSGS in three generations of a family in which an autosomal dominant pattern had been

observed. Whether this is a different subgroup of idiopathic NS remains to be elucidated. Yet many authors believe that the inheritance of familial NS is polygenic, and that environmental as well as genetic factors may play a key role in the etiology of NS[1,2,5].

Two sibs with FSG have been previously reported in the literature.

Summary

Two siblings with primary nephrotic syndrome are presented. The parents of the patients were first cousins. There was no reported history of renal disease in three generations of their family. The nephrotic syndrome developed at the age of one year in both siblings. They were both resistant to immunosuppressive treatment. The older child died of septicemia six months following the clinical appearance of the nephrotic syndrome. A renal biopsy, which was performed only on the younger child, showed typical findings of focal glomerulosclerosis.

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