Pediatr Nephrol (2000) 14:960–964 © IPNA 2000

ORIGINAL ARTICLE

S. Gulati · R. Elhence · V. Kher · R.K. Sharma
M. Jain · A. Gupta · R.K. Gupta

Early versus late-onset idiopathic focal segmental glomerulosclerosis

Received: 13 April 1999 / Revised: 24 November 1999 / Accepted: 28 November 1999

Abstract Glomerular diseases in children, although similar in histological appearance to those in adults, may have a better prognosis. There is much controversy regarding the prognostic factors in idiopathic focal segmental glomerulosclerosis (FSGS), especially the comparative prognosis of children and adults. A comparative analysis was carried out of 36 consecutive biopsy-proven cases of idiopathic FSGS presenting early in life ['early onset' as seen in children ≤12 years (group I)] and 36 cases presenting later ['late-onset' as seen in older children >12 years and adults (group II)]. Patients were compared for clinical, biochemical, and histopathological features, as well as disease outcome. A significantly higher prevalence of hypertension (P=0.002) and microscopic hematuria was seen in group II (P=0.02). There were no differences between the two groups in glomerular filtration rates corrected for body surface area at initial presentation (92±11 ml/min/1.73 m^2 vs. 94±14 ml/min/1.73 m^2). Patients with 'late-onset' FSGS had a significantly higher number of glomeruli with segmental sclerosis (P=0.007), more mesangial matrix expansion (P=0.009), greater mesangial cellularity (P=0.003), and significantly higher blood vessel involvement (P=0.03) than those with 'early onset' FSGS. There was a significantly higher response to steroids in group I (82.3%) than group II (36.4%) (P<0.02). At the end of the study period, 2 patients in group I and 11 in group II had developed persistent renal failure (P=0.01). Thus 'early onset' FSGS is more common in males, has significantly lower prevalence of hypertension and microscopic hematuria, with less-severe histopathological involvement, is more often steroid responsive, and has a better prognosis than 'late-onset' FSGS.

S. Gulati (✉) · R. Elhence · V. Kher · R.K. Sharma · A. Gupta
Department of Nephrology,
Sanjay Gandhi Postgraduate Institute of Medical Sciences,
Raebareli Road, Lucknow 226014, India

M. Jain · R.K. Gupta
Department of Pathology,
Sanjay Gandhi Postgraduate Institute of Medical Sciences,
Raebareli Road, Lucknow 226014, India

Key words Focal segmental glomerulosclerosis · Nephrotic syndrome · Renal failure

Introduction

Focal segmental glomerulosclerosis (FSGS) has posed a therapeutic challenge since it was first described more than 80 years ago. FSGS is characterized by nephrotic syndrome and progressive renal failure in the majority of cases. There have been a number of studies to define prognostic markers in idiopathic FSGS, both in children and adults. Only nephrotic-range proteinuria and serum creatinine at presentation have been consistently reported to indicate a poor prognosis [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. The data regarding the significance of other demographic, clinical, and histopathological parameters is variable and conflicting. This is especially true for the prognostic value of age [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. Glomerular diseases in children, although similar in histological appearance to those in adults, may have a better prognosis. This has been shown to be true for idiopathic membranous glomerulopathy [12, 13]. We therefore conducted a prospective study to compare idiopathic FSGS presenting early in life (as seen in children ≤12 years) with that presenting later (as seen in older children >12 years and adults), with regard to clinical features, histopathology, response to therapy, and prognosis.

Patients and method

The study group comprised 36 consecutive biopsy-proven patients with 'early onset' FSGS (group I, age of onset ≤12 years) and 36 with 'late-onset' FSGS (group II, age of onset >12 years). All study patients were diagnosed as having idiopathic FSGS at our hospital following clinical examination, biochemical investigations, and renal biopsy. They belonged to a homogenous racial group representing the Northern and Eastern Indian population.

Patients in group I were recruited into the study from a referral population of 200 children with idiopathic nephrotic syndrome over a 33-month period. All fulfilled the International Study for Kidney Disease in Childhood (ISKDC) criteria for the diagnosis

of nephrotic syndrome [14]. In the 'late-onset' group (group II), 36 patients were selected from a group of 250 adults with idiopathic nephrotic syndrome (proteinuria >3.5 g/1.73 m^2) over the same period and an additional 3 months (36 months).

After informed consent, children were biopsied in accordance with the following criteria: (1) age at onset of nephrotic syndrome less than 1 year and more than 8 years; (2) frequent relapses and steroid dependency prior to cytotoxic therapy; (3) no response to a 4-week course of prednisolone therapy; (4) the presence of two or more unusual clinical features (hypertension, gross hematuria) and/or laboratory abnormalities (abnormal renal function, low C3) [14]. All adults with nephrotic-range proteinuria (>3.5 g/1.73 m^2) were biopsied. Patients with clinical or laboratory evidence of systemic disease (post-infectious glomerulonephritis, systemic lupus erythematosus, Henoch-Schonlein purpura, IgA nephropathy, diabetes mellitus, and chronic hypertension) or anatomical disorders (reflux nephropathy, unilateral renal agenesis) were excluded from the study. The diagnosis of FSGS was based on the presence of at least a single sclerotic segment in the glomerulus with or without evidence of hyalinosis. Most patients had foci of tubular atrophy. Those with mesangial deposition of IgA or IgG in association with IgM were excluded.

Patients were assessed for the following clinical features: edema, hypertension, microscopic hematuria, and renal dysfunction. All were subjected to the following biochemical investigations: blood urea nitrogen, serum creatinine, total protein, serum albumin, and serum cholesterol.

Renal biopsies were fixed in Dubosq-Brazil fixative. Serial sections (15–20) of 2- to 3-μm were obtained after paraffin embedding and subjected to light microscopy. These were stained with hematoxylin-eosin, periodic acid-Schiff, silver methenamine, and Masson's trichrome stain and interpreted by two histopathologists independently, each of whom were blinded to the clinical outcome. Immunohistochemistry was performed after trypsin digestion for IgG, IgM, IgA, C1q, and C3. The severity of glomerular changes was assessed by calculating the percentage of glomeruli with segmental sclerosis. Other histopathological changes (mesangial matrix, mesangial cellularity, interstitial fibrosis, interstitial infiltration, tubular atrophy, and blood vessel involvement) were scored using a semi-quantitative scoring system as follows: 0=no change; 1=focal changes (<10%); 2=mild involvement (10%–25%); 3=moderate (26%–50%); 4=severe changes (>50%). This system was similar to that used in an earlier study [10]. The patients in both groups were treated with steroids and/or cyclophosphamide. Patients in group I were treated with prednisolone according to the standard 8-week APN (Arbeitsgemienschaft fur Padiatrische Nephrologie) protocol, i.e., initial attack, prednisolone 60 mg/m^2 per day for 4 weeks followed by 40 mg/m^2 on alternate days for 4 weeks; relapse, 60 mg/m^2 per day until remission, followed by 40 mg/m^2 on alternate days for 4 weeks [14]. In group II the subjects were treated with a prednisolone dose of 1 mg/kg per day for a mean duration of 16.5 weeks (range 8–24 weeks) [15]. Cyclophosphamide was administered using a dose of 2.5 mg/kg per day for 2–3 months. A subgroup of 11 patients, after obtaining consent, received intravenous cyclophosphamide as part of an ongoing study described previously [16]. All these patients were followed monthly, for a minimum period of 6 months after completion of therapy. At each follow-up visit these patients were subjected to the following investigations: serum total protein, albumin, serum creatinine, blood urea nitrogen, and a urinary protein/creatinine ratio estimation using a spot urine sample in younger children and 24-h timed urine protein and creatinine estimation in older children and adults. Glomerular filtration rate (GFR) was calculated and normalized for the body surface area in group I using the Schwartz formula [17] and in group II by the Cockfort-Gault formula [18]. At the end of the study period, the response to therapy was defined in terms of: (1) no response, i.e., persistent proteinuria (>300 mg/day in group II and >4 mg/m^2 per hour in group I); (2) partial response – remission in response to therapy (<300 mg/day in group II and <4 mg/m^2 per hour in group I) but more than two relapses over 6 months; (3) complete response – remission of proteinuria and no relapse or one relapse over a period of 6 months. These patients were also assessed for steroid side effects, including infectious complications. The two groups were compared for the following: clinical features, biochemical investigations at onset and at follow-up, response to therapy, and side effects of steroid therapy.

The time of onset of the disease was calculated from the appearance of clinical symptoms and documented proteinuria. Hypertension in children was defined as blood pressure >95th percentile for age, in accordance with the recommendations of the Second Task Force of the American Academy of Pediatrics [19]. In the 'late-onset' group, hypertension was defined as a blood pressure >140/90 mmHg in accordance with the criteria defined by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure [20]. Renal dysfunction in group I was defined as an increase in serum creatinine beyond the normal for age [21]. In group II, renal dysfunction was defined as an increase in serum creatinine >124 μmol/l. Persistent renal failure was defined as an increase in serum creatinine on follow-up by >26.5 μmol/l beyond the normal defined above in the respective groups. Patients in whom initial high serum creatinine levels decreased to within the normal range on follow-up were classified as having transient renal dysfunction.

Statistical analysis

The results were analyzed for statistical significance using Student's *t*-test and chi-squared testing. The histopathological scores in the two groups were compared using the analysis of variance (ANOVA). All values are mean±standard deviations.

Results

The 'early onset' group had 30 males and 6 females, while the 'late-onset' group comprised 17 males and 19 females. The mean age of onset of patients in group I was 6.0±4.1 years compared with 28.6±10.4 years in group II. The mean duration of disease in the two groups was similar (group I 47.1±50 months vs. group II 41.8±57 months) (P=0.01). The mean duration of follow-up following histopathological diagnosis was similar in the two groups (group I 14.6±13 months vs. group II 17.8±13 months) (P=0.3). In the 'early onset' group all had edema, 13 (36.2%) had hypertension and microscopic hematuria, and 8 (22.2%) renal dysfunction on presentation. In the 'late-onset' group, edema was the most-common feature (n=30), followed by hypertension (n=26), microscopic hematuria (n=23), and renal dysfunction (n=8). In group I, 19 children had received prednisolone alone, and 17 prednisolone and cyclophosphamide. In group II the majority of patients (n=30) were treated with prednisolone; 6 received a combination of prednisolone and cyclophosphamide. The biochemical investigations are shown in Table 1. Patients in group I had a significantly lower total serum protein and albumin (P<0.02) and higher serum cholesterol (P<0.02) than those in group II.

The histopathological scoring of both groups is shown in Table 2. Patients in group II had a significantly higher number of glomeruli with segmental sclerosis (P=0.007), more mesangial matrix expansion (P=0.009), higher mesangial cellularity (P=0.003), and significantly higher blood vessel involvement (P=0.03) than those in group I (Table 2). Immunohistochemistry was similar in

Table 1 Biochemical parameters on presentation in 'early onset' (group I) and 'late-onset' (group II) focal segmental glomerulosclerosis (*GFR* glomerular filtration rate)

	On presentation			Follow-up		
	Group I	Group II	*P* value	Group I	Group II	*P* value
Blood urea nitrogen (mmol/l)	6.0±3.6	6.1±3.7	>0.05	4.3±6.0	9.3±7.8	<0.01
Serum creatinine (mmol/l)	97±72	133±106	>0.05	88±71	177±159	<0.01
Total protein (g/l)	46±8	62±12	<0.02	61±14	63.7±9.5	>0.05
Serum albumin (g/l)	20±0.7	33±10	<0.02	33±12	34.7±7.4	>0.05
Serum cholesterol (mmol/l)	11.6±4.5	7.6±2.7	<0.02	307±210	238±113	>0.05
GFR (ml/min per 1.73 m^2)[a]	92±11	94±14	>0.05	94±12	70±24	<0.001

[a] GFR corrected for body surface area calculated by the Schwartz formula in group I and Cockfort-Gault formula in group II

Table 2 Histopathological scoring in 'early onset' and 'late-onset' focal segmental glomerulosclerosis[a]

	Group I	Group II	*P* value*
Percentage of glomeruli with segmental sclerosis	15.7±21.5 (0–1)	31.5±24.3 (0–1)	0.007
Mesangial matrix	0.24±0.43 (0–1)	0.55±0.51 (0–1)	0.009
Mesangial cellularity	0.20±0.41 (0–1)	0.55±0.51 (0–3)	0.003
Tubular atrophy	1.7±0.47 (0–2)	1.7±0.70 (0–3)	0.82
Interstitial fibrosis	0.15±0.36 (0–1)	0.42±0.85 (0–3)	0.09
Interstitial infiltration	0.56±0.70 (0–3)	0.71±0.74 (0–3)	0.40
Blood vessel involvement	0	0.29±0.78 (0–2)	0.03

*Significance calculated by analysis of variance
[a]Values are mean±SD, range in parentheses

Table 3 Therapeutic outcome in 'early onset' and 'late-onset' focal segmental glomerulosclerosis

	Group I	Group II
Complete response	17 (47.2%)	7 (19.4%)
Partial response	9 (25%)	6 (16.7%)
No response	10 (27.8%)	23 (63.9%)

P=0.01 for 'early onset' vs. 'late-onset' group as a whole

both groups, showing IgM and C3 deposits in 16 patients in group I and 20 in group II.

A significantly higher number of patients in group I responded to therapy compared with group II (*P*=0.01 for 'early onset' vs. 'late-onset' group as a whole, Table 3). Evaluation of renal function on follow-up, nearly 4 years after the onset of the disease, showed patients in group II had a significantly lower GFR corrected for body surface area than those in group I (94±12 ml/min per 1.73 m^2 vs. 70±24 ml/min per 1.73 m^2) (Table 1). During this period 2 patients in group I and 11 in group II developed persistent renal failure (*P*=0.01). Of these, 1 in group I and 3 in group II progressed to end-stage renal disease.

There was a higher prevalence of cushingoid appearance in group I than in group II (42% vs. 20%, *P*<0.02). The prevalence of other side effects of steroids (hypertension, proximal myopathy, and gastrointestinal erosions) was not significantly different. Tuberculosis was more common in group II, whilst other infections (urinary tract infections, peritonitis, pneumonia, and skin infections) were more common in group I, although the differences did not reach statistical significance.

Discussion

FSGS associated with idiopathic nephrotic syndrome frequently progresses to chronic renal failure. Several studies have been conducted to identify prognostic factors in this disease [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13]. There are conflicting data regarding the prognostic value of demographic and clinical features, particularly those comparing prognosis in children and adults [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11].

In the present study, a comparative analysis of 36 consecutive cases of idiopathic FSGS presenting in children ('early onset') and 36 older children and adults with idiopathic FSGS ('late-onset') was performed, over the same period. These patients belonged to the same ethnic group. The mean duration of disease from the onset of symptoms was similar in the two groups (*P*>0.05). The time of onset of the disease was calculated from the appearance of symptoms and documented proteinuria. It is possible however that proteinuria may have preceded the onset of symptoms, especially in group II, and hence this may only be an approximation.

There were more males in group I than in group II. Group II had a significantly higher frequency of hypertension (*P*=0.002) and microscopic hematuria (*P*=0.02) than group I. These features have been shown to be of prognostic significance in previous studies [1, 2, 13]. Also, patients in group I had a significantly lower total serum protein and albumin and a significantly higher serum cholesterol at initial presentation than those in group II (*P*<0.02). Despite these adverse prognostic features, significantly more patients in group I attained remission and had a bet-

ter prognosis compared with group II. The response rate of 47.2% in the 'early onset' group was similar to that in other studies in children [1, 5, 9, 13]. Similarly, the response rate of 19.4% in the 'late-onset' group is similar to that reported previously in adults [3, 4, 5, 13].

Comparing therapeutic response in the two groups, more patients in group I had received cyclophosphamide than in group II. This could account for the better response observed in those with 'early onset' disease. However, in most studies in adults it has been shown that addition of cyclophosphamide to prednisolone does not significantly alter response rates [15]. Patients in group I had a significantly lower percentage of glomeruli with segmental sclerosis, mesangial matrix expansion and cellularity, and blood vessel involvement compared with group II. Thus the better response rate in children appears to be an inherent characteristic of the disease with a histopathological basis [13].

There was a higher frequency of cushingoid appearance in group I and this may be related to use of a higher dose of steroids in this group of patients. The higher frequency of all infections, excluding pulmonary tuberculosis, in group I is consistent with observations made in a previous studies [22, 23]. Although the mean GFR at initial presentation was similar in the two groups (Table 1), at the end of the study the GFR was significantly lower in group II ($P<0.001$). During this period significantly more patients in group II developed persistent renal failure. This could be due to the fact that FSGS is more severe in patients with 'late-onset' disease, as reflected clinically by a higher prevalence of hypertension, microscopic hematuria, and lower remission rates. This was further substantiated by the more-severe histopathological features in this group.

It is difficult to objectively compare nephrotic syndrome in children with that in adults, as treatment schedules, definition of steroid resistance, and indications for biopsy differ. Membranous nephropathy has a better prognosis in children than in adults [12, 13]. Most authors believe that the long-term prognosis in children (corresponding to those with 'early onset' disease) is similar to that in adults, despite the well-documented higher remission rate in children [5, 6, 13]. Response to therapy has been found to have prognostic significance [1, 3]. In an actuarial analysis of 28 adults with FSGS, it was observed that the cumulative survival at 5 years was 55% and at 10 years 25% [13]. This is lower than the actuarial survival of 50%–70% at 17–19 years of follow-up in two series of biopsy-proven FSGS in children [13].

The better prognosis in children than in adults has been reported in only a few previous studies [10, 11]. However these studies have limitations with regard to their design and number of patients studied. The study of Newman et al. [10] not only involved a smaller number of patients, but also the patients in the two groups were studied over different periods of time with different durations of follow-up. Moreover only 21 of 33 patients in their study were treated with steroids [10]. In a recent study, Fogo et al. [11] demonstrated less-severe glomerular sclerosis and a better prognosis in children than in adults with idiopathic FSGS. However in this study the number of patients was also small and not all adults were treated with prednisolone [11].

Our study involved equal number of patients who were treated according to standard protocols. All were of similar ethnic background, had a similar duration of disease, and were followed concurrently at our center. Adults with idiopathic nephrotic syndrome were all biopsied. As it is unethical to subject all children with steroid-responsive nephrotic syndrome to kidney biopsies, it is possible that some of the children who were not biopsied had idiopathic FSGS. If these cases were included, it would only further increase the number of children attaining remission. This would further substantiate our findings that patients with 'early onset' idiopathic FSGS have a better prognosis.

In conclusion 'early onset' FSGS, as seen in children ≤12 years old, has a significantly lower prevalence of hypertension and microscopic hematuria, a higher remission rate in response to therapy, less-severe histological changes, and a lower frequency of persistent renal failure. Hence our findings strongly support the view that 'early onset' onset idiopathic FSGS of childhood has a better prognosis than 'late-onset' idiopathic FSGS, as seen in children >12 years and adults.

Acknowledgements The authors would like to acknowledge the services of Dr Rajendra Bhimma, Renal Fellow, Division of Nephrology, Hospital for Sick Children in reviewing this manuscript.

References

1. Schwartz MM, Korbet SM (1993) Primary focal segmental glomerulosclerosis: pathology, histological variants and pathogenesis. Am J Kidney Dis 22:874–883
2. Howie AJ, Lee SJ, Green NJ, Newbold KM, Kizaki T, Koram A, Richards NT, Michael J, Adu D (1993) Different clinicopathological types of segmental sclerosing glomerular lesions in adults. Nephrol Dial Transplant 8:590–599
3. Cameron JS, Turner DR, Ogg CS, Chantler C, William DS (1978) The long term prognosis of patients with focal segmental glomerulosclerosis. Clin Nephrol 10:213–218
4. Mongeau JG, Robitaille PO, Clermont MJ, Merouani A, Russo P (1993) Focal segmental glomerulosclerosis 20 years later from toddler to grown up. Clin Nephrol 40:1–6
5. D'Agati V (1994) Nephrology forum – the many masks of focal segmental glomerulosclerosis. Kidney Int 46:1223–1241
6. Mongeau JG, Corneille L, Robitaille P, O'Regan S, Pelletier M (1981) Primary nephrosis in childhood associated with focal glomerulosclerosis is long term that severe. Kidney Int 20: 743–746
7. Korbet SM, Schwartz MM, Lewish J (1986) The prognosis of focal segmental glomerular sclerosis of adulthood. Medicine (Baltimore) 65:304–311
8. Arora P, Pandey R, Kher V, Krishnani M, Jha R, Gupta A, Sharma RK (1992) Rapidly progressive focal segmental glomerulosclerosis. Ind J Nephrol 2:147–150
9. South West Pediatric Nephrology Study Group (1985) Focal segmental glomerulosclerosis in children with idiopathic nephrotic syndrome. Kidney Int 27:442–449
10. Newman WJ, Tisher CC, McCoy RC, Gunnells JC, Krueger RP, Clapp JR, Robinson RR (1978) Focal glomerulosclerosis, contrasting clinical patterns in children and adults. Medicine (Baltimore) 55:67–87

11. Fogo A, Glick AD, Horn SL, Horn SG (1995) Is focal segmental glomerulosclerosis really focal? Distribution of lesions in adults and children. Kidney Int 47:160–166
12. Pierides AM, Malasit P, Morley AR, Wilkinson R, Uldall PR, Kerr DMS (1977) Idiopathic membranous nephropathy. Q J Med 22:874–883
13. Trompeter RS, Barratt TM (1998) Treatment and management of the nephrotic syndrome in children In: Cameron JS, Glassock RS (eds) The nephrotic syndrome. Dekker, New York, pp 423–460
14. Gulati S, Kher V, Sharma RK, Gupta A (1994) Steroid response pattern in Indian children with nephrotic syndrome. Acta Paediatr Scand 83:530–533
15. Glassock RJ (1993) Therapy of idiopathic nephrotic syndrome in adults. Am J Nephrol 13:422–428
16. Elhence R, Gulati S, Kher V, Gupta A, Sharma RK (1994) Intravenous pulse cyclophosphamide: a new regime for steroid resistant minimal change nephrotic syndrome. Pediatr Nephrol 8:1–3
17. Toto RD(1995) Conventional measurement of renal function utilizing serum creatinine, creatinine clearance, inulin and para-aminohippuric acid clearance. Curr Opin Nephrol Hypertens 4:505–509
18. Schwartz GJ, Brion LP, Spitzer A (1987) The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am 34:571–590
19. Report of the Second Task Force on Blood Pressure Control in Children (1987) Pediatrics 79:3–27
20. The Joint National Committee (1997) The sixth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 157: 2413–2446
21. Schwartz GJ, Haycock GB, Spitzer A (1976) Plasma creatinine and urea in children: normal values for age and sex. J Pediatr 88:828–830
22. Broyer M, Meyrier A, Niaudet P, Habib R (1998) Minimal change and focal glomerulosclerosis. In: Davison AM, Cameron JS, Grunfeld JP, Kerr DNS, Ritz E, Winerals CS (eds) Oxford Textbook of Clinical Nephrology. Oxford University Press, Oxford, pp 493–535
23. Cameron JS (1998) Clinical consequences of the nephrotic syndrome. In: Cameron S, Davison AM, Grunfeld JP, Kerr D, Ritz E (eds) Oxford Textbook of Clinical Nephrology. Oxford University Press, Oxford, pp 276–297

LITERATURE ABSTRACTS

M.E. Taekema-Roelvink · C. Van Kooten · E. Heemskerk W. Schroeijers · M.R. Daha

Proteinase 3 interacts with a 111-kD membrane molecule of human umbilical vein endothelial cells

J Am Soc Nephrol (2000) 11:640-648

Proteinase 3 (PR3) is the major autoantigen of antineutrophil cytoplasmic antibodies in Wegener's granulomatosis. Previously, it was demonstrated that PR3 induces apoptosis of human endothelial cells and that PR3 contributes to endothelial cell activation by enhancing interleukin-8 production. The present study demonstrates that PR3 binds specifically to human umbilical vein endothelial cells (HUVEC). Digoxigenin (DIG)-labeled PR3 bound readily to HUVEC cultured on coverslips. By fluorescence-activated cell sorter analysis, a homogeneous binding of PR3 to HUVEC, using either DIG-labeled or unlabeled PR3, was observed. No detectable membrane expression of PR3 was observed after either tumor necrosis factor-alpha stimulation or in nonstimulated HUVEC. The binding of PR3-DIG to HUVEC was dose-dependent and was inhibited by unlabeled PR3. Scatchard analysis revealed 2000 binding sites per cell, with a Kd of 0.1 microM. Affinity precipitation of biotin-labeled HUVEC membrane proteins with protein G-Sepharose bearing PR3 resulted in specific precipitation of a membrane molecule with a molecular weight of 111 kD under nonreducing conditions and 52 and 63 kD under reducing conditions. It is hypothesized that PR3, either released systemically or locally at inflammatory sites following activation of primed polymorphonuclear neutrophils, may lead to endothelial cell injury and activation of endothelial cells.

J.P. Haymann · J.P. Levraud · S. Bouet · V. Kappes · J. Hagege G. Nguyen · Y. Xu · E. Rondeau · J.D. Sraer

Characterization and localization of the neonatal Fc receptor in adult human kidney

J Am Soc Nephrol (2000) 11:632-639

The binding of Fc fragments of Ig on glomerular epithelial cells (GEC) was observed previously, but the receptor could not be identified. In immunofluorescence and immunohistochemical studies using normal adult human kidney sections, the presence of the so-called neonatal Fc receptor (FcRn) demonstrated on GEC as well as in the brush border of proximal tubular cells. FcRn transcripts were also detected on isolated glomeruli by reverse transcription-PCR. Using an immortalized GEC line, the presence of the FcRn was confirmed by flow cytometry, reverse transcription-PCR, Western blotting, and by the pH dependence of the binding of heat-aggregated IgG. Because it is established that the FcRn is involved in IgG transcytosis, it is hypothesized that the FcRn in the kidney may play a role in the reabsorption of IgG. Ongoing studies should clarify the role of the FcRn as a potential target for immune complexes on GEC and should assess its relevance in physiology and pathology.