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Original article

Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisolone and alkylating agents

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Abstract. In children, steroid-resistant nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS) is frequently a progressive condition resulting in end-stage renal disease. There have been no reports of effective treatment for this condition. For the past several years, the Pediatric Nephrology services at the University of California, San Diego and Stanford University Schools of Medicine have treated these patients with a protocol involving infusions of high doses of methylprednisolone, often in combination with oral alkylating agents. Twenty-three children have been treated in this manner with a follow-up of 46 ± 5 months. Twelve of these children are in complete remission. Six have minimal to moderate proteinuria. Four children remain nephrotic. Each of these children has a normal glomerular filtration rate. One child developed chronic renal failure and subsequently died while on dialysis. These results appear significantly better than previous series of children with FSGS. A controlled, multi-center trial of this protocol has been proposed.

Key words: Nephrotic syndrome – Focal segmental glomerulosclerosis – Chronic renal failure – Methylprednisolone – Alkylating agents – Proteinuria

Introduction

Focal segmental glomerulosclerosis (FSGS) is a cause of steroid-resistant nephrotic syndrome and chronic renal failure (CRF) in childhood. It is often a progressive condition with a poor prognosis [1–6]. Overall, the incidence of renal failure is 25–30% by 5 years after the onset of FSGS and 30–40% after 10 years [7]. FSGS is the most common form of glomerular disease leading to CRF in children [8] and is seen in 10–20% of children requiring dialysis or renal transplantation [9]. In recent years, the Pediatric Nephrology services at the Stanford and University of California, San Diego Schools of Medicine have treated these children with a protocol involving intravenous infusions of high doses of methylprednisolone, often in association with oral alkylating agents. Preliminary results on seven patients were described previously [10]. We now report the outcome of the first 23 patients treated in this way and followed for 46 ± 5 months.

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Methods

Each of the patients included in this report presented with the nephrotic syndrome. Each patient had marked proteinuria, edema, hypoalbuminemia and hyperlipidemia. The patients remained nephrotic after 4–8 weeks of treatment with oral prednisone at a dose of 2 mg/kg per day. Renal biopsy which was performed on each patient revealed FSGS. Information regarding the age at onset, whether the patients were steroid-resistant at the time of initial presentation (primary steroid-resistance) or later in their course (secondary steroid-resistance), and pre-treatment urinary protein/creatinine and creatinine clearance is included in Table 1. Patient 22 had a brother who had died at another medical center with FSGS. Patient 20 had cyanotic congenital heart disease corrected by a modified Fontan procedure. He had proteinuria before the surgery.

When the diagnosis of steroid-resistant nephrotic syndrome and FSGS was made, methylprednisolone therapy was offered. In 2 patients, the treatment was refused by the families. The remaining patients were started on a protocol of methylprednisolone infusions (30 mg/kg per dose). Since this was a retrospective study, there were minor differences in the protocol from patient to patient. The protocol which was used most often is shown in Table 2. In some cases, the initial six methylprednisolone infusions were given while the child was hospitalized. In most cases, all of the infusions were given by a nephrology nurse in an outpatient setting. While the patients were receiving methylprednisolone infusions, they also were given oral prednisone (2 mg/kg every other day). If the patients either failed to respond to the initial 10 weeks of methylprednisolone infusions or, improved but subsequently relapsed, methylprednisolone therapy was recommenced and they were given an 8- to 12-week course of therapy with an oral alkylating agent (cyclophosphamide 2 mg/kg per day or chlorambucil 0.2 mg/kg per day). Fifteen patients had at least one course of therapy with an alkylating agent. One child remained nephrotic but did not receive an alkylating agent at the request of the parents. A number of patients received more than one course of treatment with alkylating agents. In general, multiple courses of

Table 1. Initial and follow-up data on patients with focal segmental glomerulosclerosis (FSGS)

Patient	Age at onset (years)	Steroid resistance	Follow-up (months)	Courses of alkylating agents	Urinary protein/creatinine[a]		Estimated GFR ml/min per 1.73 m^2 [P_{Cr}]	
					Initial	Final	Initial	Final
1	3 11/12	Primary	95	0	22.0	1.41	83 [0.7]	169 [0.5]
2	1 2/12	Primary	88	0	29.4	0.35	145 [0.3]	118 [0.6]
3	7 3/12	Secondary	78	2	13.4	0.007	215 [0.3]	110 [0.8]
4	2 4/12	Secondary	78	4	6.0 g	0.45	84 [1.3]	132 [0.7]
5	8 1/12	Primary	72	1	7.4	0.0	118 [0.6]	108 [0.8]
6	9 6/12	Primary	68	0	12.4	0.12	114 [0.8]	87 [1.0]
7	6 5/12	Secondary	66	3	4.8	0.07	148 [0.5]	142 [0.6]
8	4 7/12	Primary	63	6	5.8	0.20	106 [0.3]	117 [0.3]
9	8 6/12	Primary	55	2	6.7	0.0	89 [0.4]	273 [0.3]
10	6 5/12	Secondary	51	1	12.1	0.12	224 [0.3]	107 [0.7]
11	16 4/12	Primary	47	0	11.5 g	0.0	90 [1.0]	114 [0.8]
12	2	Primary	42	1	39.7	Deceased	99 [0.3]	0
13	13 11/12	Primary	35	2	10.6	0.17	173 [0.5]	158 [0.6]
14	13 6/12	Primary	30	0	6.5	0.0	128 [0.7]	101 [0.9]
15	1 3/12	Primary	29	1	3.8	0.25	90 [0.5]	107 [0.5]
16	15	Primary	28	0	17.9	3.56	90 [1.0]	91 [1.2]
17	3 1/12	Primary	21	1	20.0	0.08	88 [0.7]	210 [0.3]
18	5 6/12	Primary	20	2	13.3	5.2	92 [0.7]	100 [0.7]
19	4 8/12	Secondary	20	Partial	5.5	0.06	119 [0.6]	149 [0.5]
20	10 6/12	Primary	19	1	8.7	9.7	77 [0.8]	110 [0.6]
21	12 3/12	Primary	18	0	6.7	1.81	182 [0.5]	176 [0.5]
22	11 9/12	Primary	15	1	21.2	13.0	138 [0.5]	142 [0.5]
23	7 10/12	Primary	10	1	4.5	0.43	344 [0.2]	242 [0.3]
Mean	7.6		46		13.0	1.68	132 [0.6]	133 [0.6]
SD	4.6		26		9.3	3.43	62 [0.27]	56 [0.23]

GFR, Glomerular Filtration rate; P_{Cr}, plasma creatinine

[a] Both urinary protein and creatinine concentrations were measured in mg/dl. In 2 cases the ratio was not available and data are presented as g/24 h

alkylating agents were given when a patient improved with the first course and subsequently relapsed. These data are also included in Table 1.

The patients were seen frequently while they were receiving methylprednisolone and/or an alkylating agent. In addition to routine clinical evaluation, serum creatinine and protein/creatinine in the urine were measured and, in many cases, 24-h urine collections for measurement of creatinine clearances and protein excretion were carried out. The glomerular filtration rate (GFR) was estimated using the height formula of Schwartz et al. [11, 12]. A GFR greater than 80 ml/min per 1.73 m^2 was interpreted as normal. The magnitude of proteinuria was assessed by comparing the urinary concentrations of protein (mg/dl) and creatinine (mg/dl) [13, 14]. A urinary protein/creatinine of less than or equal to 0.20 was considered to be normal; a ratio of 0.21 – 0.5 was designated minimal proteinuria; a ratio of 0.51 – 2.0 was interpreted as moderate proteinuria and a ratio of greater than 2.0 was consistent with nephrotic levels of proteinuria. Data are presented as mean ± SD. Statistical comparisons were made using chi-square analysis with Yates' correction.

Table 2. Usual treatment protocol for FSGS

Week	Methylprednisolone	Prednisone
1	30 mg/kg every other day (X3)	None
2	30 mg/kg every other day (X3)	None
3 – 10	30 mg/kg weekly	2 mg/kg every other day
11 – 18	30 mg/kg every other week	2 mg/kg every other day
19 – 52	30 mg/kg monthly	2 mg/kg every other day
53 – 78	30 mg/kg every other month	2 mg/kg every other day

Methylprednisolone is then discontinued and oral prednisone tapered and discontinued

Results

We treated a total of 23 patients with steroid-resistant nephrotic syndrome and FSGS with methylprednisolone infusions. They first developed the nephrotic syndrome at 7.6 ± 1.0 years of age. Sixteen of the patients were male; 7 were female. Eighteen patients were steroid-resistant at the time that the diagnosis of nephrotic syndrome was made. The remaining 5 patients were initially steroid-responsive, but later relapsed and failed to respond to oral prednisone. Two patients (nos. 4, 21) had initial biopsies which did not show FSGS. Patient 4 had a biopsy 8 years after the onset of his nephrotic syndrome which was read as minimal change nephrotic syndrome. About 18 months later, he became resistant to oral steroids and a repeat biopsy showed FSGS. Patient 21 had mesangial proliferation on a renal biopsy carried out at the onset of her disease when she did not respond to oral prednisone therapy. Four years later, a second biopsy showed FSGS and she was started on

Table 3. Side effects of the FSGS treatment protocol

Side effect	No. of patients
Cataracts	5/23
Slowed growth	4/23
Nausea	Common
Hypertension	4/23
Leukopenia	3/16

methylprednisolone. The remaining 21 patients had FSGS on the first renal biopsy. In each case, the indication for performing the renal biopsy was steroid resistance. Since we usually do not carry out renal biopsies on children with nephrotic syndrome who respond to prednisone, there is no information regarding the initial renal histology of the remaining 4 patients who were steroid-responsive.

The mean follow-up of these patients is 46 ± 5 months. Their status at their most recent follow-up is summarized in Table 1. Twenty-two patients had a normal estimated GFR. One child progressed to end-stage renal disease (ESRD) and subsequently died. Twelve patients were in complete remission (after 20–78 months). Nine of these were receiving no treatment when last seen. Four patients had minimally elevated urine protein excretion; 2 had moderately elevated urinary protein excretion; and 4 children continued to have nephrotic levels of proteinuria. Three of the nephrotic children (patients 16, 18, 22) had a significantly lower urinary protein excretion at the time of their most recent follow-up than they had before starting the methylprednisolone protocol. Only patient 20 had no decrease in urinary protein excretion.

Side effects of the methylprednisolone therapy have been minimal to date, although no information is available regarding long-term side effects, such as sterility and oncogenesis (Table 3). Five patients developed small cataracts while receiving this treatment. A number of children reported nausea during the methylprednisolone infusions. This was particularly common when the interval between infusions was 1 month or longer. Growth has been good in most of these patients. However, patients 3, 4, 5, and 7 had significant slowing of growth while receiving frequent methylprednisolone infusions, alternate-day oral prednisone and several courses of treatment with oral alkylating agents. Eventually, each of these children went into a prolonged remission of the nephrotic syndrome. Patient 3 subsequently had a period of "catch-up" growth. Patients 4, 5, and 7 remain growth-retarded. As noted above, patient 20 had cyanotic congenital heart disease. He was two standard deviations below the 5th percentile for height at the time he developed the nephrotic syndrome. He has continued to grow along the same height curve during treatment of FSGS. Patient 22 was nearly three standard deviations below the 5th percentile for height at the time he developed the nephrotic syndrome. He has also continued to grow along his own height curve while receiving methylprednisolone and alkylating agent therapy.

Fatal infections have been reported in patients treated with methylprednisolone [15]. Four of our patients had an episode of bacterial peritonitis or sepsis before starting methylprednisolone. Two patients had peritonitis while on this treatment. One patient had herpes zoster and another patient had cellulitis of the leg while receiving methylprednisolone. All patients recovered from these infections uneventfully. Four patients developed hypertension which required therapy during the protocol. The hypertension was easily controlled and resolved as the interval between methylprednisolone infusions increased. Other complications of high-dose steroid therapy such as striae, aseptic necrosis of the femoral head, diabetes and pancreatitis were not observed. No major adverse effects of alkylating agents were observed. Three patients developed transient leukopenia during treatment with alkylating agents, which led to an interruption of the treatment. In each case, the therapy was completed when the white blood count rose to the normal range.

Discussion

The prognosis of children with FSGS is generally poor [1–6]. It is estimated that 10–20% of children who progress to dialysis or transplantation have FSGS [9]. In fact, FSGS is the most common form of glomerular disease leading to CRF in children [8]. In addition, there is a significant risk of recurrence of FSGS following renal transplantation [8, 9, 16].

In some series of children with FSGS, the prognosis of primary steroid-resistant patients and late steroid non-responders was equally poor [2, 4]. Other authors have reported that patients with FSGS and primary steroid resistance progress to renal failure faster than late non-responders [5]. Five of our 23 patients responded to oral steroid therapy early in the course of their disease and subsequently became steroid-resistant. The remaining 18 patients were steroid-resistant at the onset of their illness.

The effect of alkylating agents on steroid-resistant FSGS is somewhat controversial. Several groups, including the International Study of Kidney Disease in Children, reported that cyclophosphamide does not improve the outcome in steroid-resistant children with FSGS [17, 18]. In contrast, it has been reported that many children with FSGS and steroid-resistant nephrotic syndrome partially respond to cyclophosphamide which leads to an improved prognosis [19]. Recently, there has been interest in the use of cyclosporine A in the treatment of FSGS. Preliminary results with this agent have been disappointing, although somewhat variable [20–24].

We have reported previously that the initial response to the treatment of steroid-resistant nephrotic syndrome and FSGS with methylprednisolone infusions appeared favorable [10]. Seven patients had been treated. In each case, there was clear improvement clinically, with disappearance of edema and improvement in serum and urine chemistry within a short time after starting methylprednisolone therapy.

After a follow-up period of 46 ± 5 months, 52.2% of our 23 patients are in complete remission, 17.4% have minimal proteinuria, 8.7% have moderate proteinuria with no edema or hypoproteinemia, 17.4% remain nephrotic, and only 1 child (4.4%) has developed ESRD. The out-

Table 4. Comparison of current and previous series

Series	No. of patients	Follow-up (months)	ESRD or death	Remission
Habib [1]	64	61	31.2%	20.3%
Ito et al. [28]	27	73	29.6%	Not known
Arbus et al. [4]	32	56	53.1%	Not known
SPNSG[a] [2]	75	57	21.0%	11.0%
SPNSG[b] [2]	45	<48	15.6%	≤ 17.8%
Tejani et al. [5]	24	114	62.5%	Not known
Ellis et al. [29]	32	62	37.5%	18.8%
Cameron et al. [6]	12	Not known	75.0%	0
Current series	23	46	4.4%	52.2%

SPNSG, Southwest Pediatric Nephrology Study Group; ESRD, end-stage renal disease.

[a] All patients in the series

[b] The subgroup of patients followed for less than 4 years. The incidence of remission in this group is not given. If all 8 patients in remission in the series were followed <48 months, the incidence would be 17.8%. Thus, the actual incidence is ≤ 17.8%

come of our prednisone-resistant patients is compared to that of other series of children with FSGS (Table 4) including both prednisone-responsive and prednisone-resistant patients. Our patients had a markedly lower incidence of ESRD and a markedly higher incidence of remission than any of these series. The mean duration of follow-up of our patients is somewhat shorter than the other series included in Table 4. For this reason, the subgroup of patients followed for less than 48 months by the Southwest Pediatric Nephrology Study Group, is also included in Table 4.

Side effects of the methylprednisolone therapy have not been severe. Five patients developed small cataracts which do not affect vision. Each of these children had been treated with high doses of daily prednisone before starting methylprednisolone infusions. In 1 child, the cataract improved after the child went into remission and treatment was discontinued. We have not seen cardiac arrhythmias following methylprednisolone infusions, although these have been reported by others [25, 26], nor did we observe allergic reactions [27]. We have seen a mild anaphylactoid reaction to methylprednisolone in a patient receiving the drug for a different reason, and we are aware of one child with FSGS who had a similar allergic reaction to intravenous methylprednisolone (N. J. Siegel, personal communication).

In summary, this group of children with FSGS has done extremely well following treatment with intravenous methylprednisolone. The outcome in this retrospective study is significantly better than all series we reviewed of children with steroid-resistant nephrotic syndrome and FSGS. Since FSGS is a common cause of ESRD in children, it is important to determine whether this treatment improves the prognosis of these patients. This can only be done with a randomized, controlled clinical trial. The authors are organizing such a multi-center trial. If this protocol does decrease the incidence of renal failure in childhood FSGS, it would be a major contribution to the welfare of these children as well as significantly decreasing the long-term cost of their care.

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Ask the expert*

What is the cause of sodium retention in acute nephritis?

Key word: Sodium retention

Nephritis is associated with increased sodium (Na) reabsorption and positive external Na balance, which underlies some of its characteristic clinical features, including peripheral edema, systemic hypertension and pulmonary congestion. It is known that during the active phase of Na retention in nephritis, plasma volume is expanded. Furthermore, disorders which cause nephritis typically do not lead to cardiac decompensation and cardiac output is most often found to be increased. There is also experimental support that intrarenal, rather than systemic circulating hemodynamic, derangements cause impairment of Na excretion. Thus, in models of unilateral nephritis, only the affected kidney exhibits depressed Na excretion. Overall, these observations indicate that the mechanisms for the positive Na balance in nephritis relate to decreased ability of the kidneys to excrete Na and represent changes within the glomerulus and the tubules [1, 2].

A decreased glomerular filtration rate (GFR) is characteristic of nephritis and reflects arteriolar vasoconstriction and inflammatory changes, which impair the permeability of the glomerular capillary bed. It should be noted that a gradual decrease in GFR may not be associated with a decrease in Na excretion because of compensatory hyperfiltration and an increase in the fractional excretion of Na by the remaining intact glomeruli. However, in acute nephritis, GFR is decreased, which is associated with decreased Na excretion. This decrease in GFR, at least in the early phase, is accompanied by relatively intact tubule function. Thus, early in the course of glomerulonephritis, as well as in the early stages of acute interstitial nephritis, urine Na values and fractional excretion of Na are low. Taken together, these observations indicate that, impairment of Na excretion in nephritis is due to a decrease in the quantity of filtrate formed by the glomerulus, combined with enhanced tubular Na reabsorption.

The decrease in GFR with the relative preservation of tubule reabsorption which are apparent in acute nephritis represent disruption of the proportionality between changes in GFR and the rate of tubule reabsorption, termed glomerulotubular balance. The site of this enhanced tubule reabsorption has not been conclusively established. Within the proximal tubule experimental studies of nephritis have found an increased, decreased or unchanged tubule reabsorption depending on the relative impact the nephritic process has on the GFR versus renal plasma flow (RPF), i. e., filtration fraction. Thus, if the decrease in RPF is proportionally greater than GFR, the filtration fraction will increase, which then serves to increase the postglomerular oncotic pressure, favoring increased reabsorption. Conversely, a more profound decrease in the GFR than RPF will lead to the opposite hemodynamic changes and decreased proximal tubule reabsorption. In experimental nephritis characterized by variability in the severity of glomerular hypofiltration, glomerulotubular balance was found to be maintained from nephron to nephron. These and other experimental models, as well as patient studies, suggest that the proximal tubule does not contribute in a significant way to enhanced Na reabsorption. Instead, it is generally believed that the distal nephron segments, and/or deeper nephrons are the sites for continued Na reabsorption in nephritis. The mechanisms for the relatively enhanced tubule reabsorption include all the factors which normally regulate Na reabsorption, such as intrarenal blood flow distribution, renin-angiotensin-aldosterone system, and sympathetic tone. However, a definitive causal role for any of these factors has not been determined in nephritis.

It should be noted that the low fractional excretion of Na is only seen early in the course of glomerulonephritis. With time, however, tubule reabsorption capacity fails, as evidenced by a high urinary Na level and fractional excretion of Na. Since tubules receive all of their blood supply from the parent glomerulus, damage/impairment of this structure will, over a short period of time, compromise the nutritive blood flow and may cause tubule damage. This tubule impairment will then lead to depressed tubule reabsorptive function and the appearance of greater amounts of Na in the urine. At this point, limitation of the renal capacity for Na excretion is related primarily to the severity of the glomerular lesion and the extent of hypofiltration.

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*The editors invite questions for this section