Correlation Between Prognosis and Response to Treatment
in Children with FSGS

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Abstract- To determine the prognostic value of response to treatment in patients with focal segmental glomerulosclerosis. FSGS includes 10-15% of idiopathic Nephrotic syndrome in children. Bulk of evidence supports disease relationship with immune system. Unfortunately, responses to immunosuppressive drugs are not desirable and progression to end-stage renal disease is common. We analyzed 62 out of 99 cases of biopsy proven idiopathic FSGS who were followed for at least 5-years or until renal failure occurred during study. Study design was historical cohort and patients were divided into two groups: exposed (resistant to treatment) and non-exposed (responsive to treatment). Correlation between prognosis and response to treatment was statistically evaluated. P-value (0.05 and relative risk ( 1 was considered significant. In 3 out of 25 steroid responsive patients (12%) and 22 out of 37 steroid resistant patients (59.5%), disease progressed to renal failure. Disease progressed to renal failure in 2 out of 11 cyclophosphamide responsive patients (18.1%), 17 out of 23 cyclophosphamide resistant patients (74.3%), and 8 out of 14 cyclosporine resistant patients (57.1%). 2 patients who responded to cyclosporine had normal renal function at the time of the last follow up. We concluded that favorable response to steroid and cyclophosphamide treatment is a protective factor against disease progression to end stage renal disease and resistance to these drugs imply a poor prognosis. For making any definite conclusion concerning response to cyclosporine treatment and prognosis, similar studies with a larger sample are required.

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Key words: Children, nephrotic syndrome, glomerulosclerosis, focal segmental, drug resistant, prognosis, steroids.

Introduction

Focal Segmental Glomerulosclerosis (FSGS) includes 10-15% of idiopathic nephrotic syndromes in children. Although pathogenesis is unknown, new studies suggest the role of podocytes disturbances in pathogenesis of disease (1). Recent data demonstrate differences between the basic pathophysiology of FSGS and minimal change nephrotic syndrome (MCNC). FSGS appears to be a podocytes disease (2). Although several published papers show a relationship between disease and immune system, response to immunosuppressive drugs is variable. FSGS includes 3% of steroid sensitive and 47.5% of steroid resistant idiopathic nephrotic syndrome (3). Clinical symptoms in FSGS are nonspecific and include edema, hypertension and sometimes gross hematuria. Urine analysis shows proteinuria with or without hematuria. The glomerular lesions affect a variable proportion of glomeruli. Focal changes are limited to a part of glomerular tuft and segmental lesions affect a few capillary loops (3-6).

Tubular atrophy and interstitial fibrosis are often present (3,4,7). On immunofluorescence, the segmental lesions may show strong staining with anti-IgM and anti C3 anti-sera. Familial cases have been reported with autosomal dominant modes of inheritance (8-10). Different immunosuppressive drugs may be used for treatment including glucocorticoids, cyclophosphamide, cyclosporine, methyl prednisolone pulse, chlorambucil and recently FK506 (3,11-16). Patients with steroid resistant nephrotic syndrome (SRNS) are at risk for developing end-stage renal disease (ESRD). ESRD developed in at least 50% of patients with SRNS.3 Progression to ESRD has been reported to be more rapid in patients of African or Hispanic descent when compared with whites (17).
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Patients and Methods

We prospectively studied 62 patients with biopsy proven idiopathic FSGS admitted to pediatric medical center of Tehran between 1986-2002.

The patients' ages were between 3 months to 14 years (mean age 4 years and 8 months). 24 patients were female and 38 patients were male (M/F = 1.6/1).

All patients were followed for at least 5 years or until renal failure occurred during follow up. The patients were followed for a period between 3 months to 16 years and 4 months (mean 7 years and 2 months).

As the first line treatment, all patients received prednisolone 2 mg/kg daily for 4 weeks (before or after renal biopsy) and subsequently 2 mg/kg in alternate days which was tapered slowly in 3 to 6 months. In steroid resistant patients after obtaining informed consent from the parents, cyclophosphamide was administered at the dosage of 2 mg/kg for 12 weeks or 3 mg/kg for 8 weeks.

We prescribed cyclosporine at the dosage of 5 mg/kg daily for 12 months in conjugation with low dose steroid to 3 groups of patients: those whose parents failed to accept cyclophosphamide (mainly because of gonadal toxicity), steroid dependent patients, steroid and cyclophosphamide resistant patients.

Patients were followed by nephrology clinic at first weekly, then every other week or monthly and every 1-3 months after remission.

In each visit, the patients were checked for edema, hypertension and infection and urine samples were analyzed for proteinuria by dipstick-test. If proteinuria was present, 24 hour urine proteins or protein-creatinine ratio in random urine samples were measured. Serum creatinine was checked every 3-6 months. In patients who received cyclosporine, serum creatinine level checked weekly in the first month, then every 2 weeks for 6 months and monthly afterward.

The study design was historical cohort and the patients were divided into two groups:

Exposed group (resistant to treatment) and non-exposed group (sensitive to treatment).

Correlation between variables (response to steroid, cyclophosphamide and cyclosporine) and prognosis was statistically analyzed. P-value (0.05 and relative risk (RR) > 1) was considered significant.

We defined normal renal function at final follow-up as good prognosis and decreased renal function (permanent rising of serum creatinine level) as poor prognosis. The patients were considered cyclophosphamide or cyclosporine resistant if proteinuria continued after a full course of treatment.

Results

25 out of 62 patients (40.3%) were steroid sensitive and 37 out of 62 patients (59.7%) were steroid resistant. 35 out of 62 patients received cyclophosphamide of whom 12 (34.2%) and 23 (65.8%) were cyclophosphamide sensitive and cyclophosphamide resistant, respectively. 16 out of 62 patients received cyclosporine of whom 2 (12.5%) responded to cyclosporine and 14 (87.5%) were cyclosporine resistant. Table 1-3 and figure 1 show the correlation between renal function and response to treatment. Comparison between drug responsive and drug resistant groups showed statistically significant difference (P-value for steroid, cyclophosphamide and cyclosporine were 0.00019, 0.00346 and 0.46 respectively). Relative risk of renal failure in steroid and cyclophosphamide resistant patients were greater than 1 (RR>1). Table 4 shows patients at final follow-up

| Table 1. Response to steroid and prognosis |

<table>
<thead>
<tr>
<th>Response to treatment</th>
<th>Renal failure</th>
<th>Good renal function</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent %</td>
<td>Number</td>
</tr>
<tr>
<td>Steroid sensitive</td>
<td>3</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Steroid resistant</td>
<td>22</td>
<td>59.5</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>40.3</td>
<td>37</td>
</tr>
</tbody>
</table>

P-value = 0.00019

| Table 2. Response to cyclophosphamide and prognosis |

<table>
<thead>
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<th>Response to treatment</th>
<th>Renal failure</th>
<th>Good renal function</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent %</td>
<td>Number</td>
</tr>
<tr>
<td>Cyclophosphamide sensitive</td>
<td>2</td>
<td>16.1</td>
<td>10</td>
</tr>
<tr>
<td>Cyclophosphamide resistant</td>
<td>17</td>
<td>73.9</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>54.3</td>
<td>16</td>
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</tbody>
</table>

P-value = 0.00346


Table 3. Response to cyclosporine and prognosis

<table>
<thead>
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<th>Response to treatment</th>
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<th>Good renal function</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent %</td>
<td>Number</td>
</tr>
<tr>
<td>cyclosporine sensitive</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>cyclosporine resistant</td>
<td>8</td>
<td>57.1</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>50</td>
<td>8</td>
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</tbody>
</table>

P-value = 0.466

Table 4. Clinical course of the disease in our patients

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>23</td>
<td>37</td>
</tr>
<tr>
<td>Persistent NS + normal renal function</td>
<td>14</td>
<td>22.6</td>
</tr>
<tr>
<td>CRF ( needed to symptomatic treatment )</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>ESRD</td>
<td>14</td>
<td>22.6</td>
</tr>
<tr>
<td>Kidney transplantation with good graft function</td>
<td>5</td>
<td>8.1</td>
</tr>
<tr>
<td>Death Due to complications of renal failure</td>
<td>4</td>
<td>6.5</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>100</td>
</tr>
</tbody>
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Discussions

In the early stage, FSGS and MCNS are indistinguishable (18) and a significant number of patients with FSGS respond favorably to glucocorticoid therapy (19).

Different studies have been conducted to clarify different therapeutic factors that affect outcome in patients with nephrotic syndrome.

It has been shown that response to steroid therapy carries a greater prognostic value than the histological features seen on the initial renal biopsy (20,21).

Hafeez et al reported a limited response to cyclosporine in patients with FSGS (22). On the contrary, other studies showed that a more prolonged use of corticosteroid and early introduction of cyclosporine A may improve the prognosis for primary FSGS and suggested cyclosporine A as a good therapeutic option for SRNS (21-23).

Lyengar reported higher risk of CRF in patients who didn't respond to cyclosporine A (24) and Geary reported less frequency of renal failure in patients who responded to cyclophosphamide (15) Other studies have reported resistance to steroid or cyclosporine as poor prognostic factors (19,20).

Our study showed that renal failure is significantly more frequent in steroid and cyclophosphamide resistant patients (P<0.05) and positive response to these drugs improved the prognosis dramatically. So we suggest steroid in all cases of FSGS and cyclophosphamide in steroid resistant cases as the second step of treatment despite its gonadal toxicity. About correlation between cyclosporine response and prognosis, Because of the small sample of patients who received cyclosporine, we cannot draw a clear conclusion considering the value of cyclosporine in FSGS patients. Further studies with a larger sample of patients are recommended.

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References

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