Treatment of Childhood Nephrotic Syndrome

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ABSTRACT

This review examines selected aspects of the treatment of the nephrotic syndrome in children. Particular attention has been paid to two groups of nephrotic children. First, children with steroid-responsive nephrotic syndrome are discussed. Recently, a series of controlled studies have provided important information regarding the optimal duration of steroid therapy. Initial episodes of the nephrotic syndrome are best treated with "long" courses of prednisone therapy (6 wk of high-dose daily prednisone followed by 6 wk of alternate-day prednisone). In contrast, relapses do as well with "short" courses (about 2 wk of daily prednisone and 2 wk of alternate-day therapy). Some children who are steroid responsive require high doses of prednisone to remain in remission. These patients may require alkylating agent therapy. The most common cause of steroid-resistant nephrotic syndrome is focal segmental glomerulosclerosis. Over the past 10 yr, these patients have been treated with an intensive protocol involving multiple infusions of high-dose methylprednisolone and, in many cases, oral alkylating agent therapy. Current experience with this treatment is presented. The protocol appears to improve the outcome in children with focal segmental glomerulosclerosis, although it is believed that it is essential that these observations be confirmed by a controlled trial. There is also interest in the use of angiotensin-converting enzyme inhibitors and cyclosporine in the treatment of childhood nephrotic syndrome. The experience with these agents is briefly reviewed, but the current data are inadequate to indicate their role(s) in this condition.

Key Words: Nephrotic syndrome, child, focal segmental glomerulosclerosis, pulse methylprednisolone therapy, cyclosporine, angiotensin-converting enzyme inhibitor

This review will examine selected aspects of the treatment of the nephrotic syndrome in children. We will focus primarily on two groups of children with the nephrotic syndrome, those who go into remission when treated with oral prednisone and those with focal segmental glomerulosclerosis (FSGS), the most common form of steroid-resistant nephrotic syndrome in children.

CHILDHOOD NEPHROTIC SYNDROME

Most children with nephrotic syndrome have minimal change histology, and the great majority of these respond to treatment with oral prednisone. The incidence of minimal change nephrotic syndrome (MCNS) varies with the age at the onset of the disease. Between the ages of 1 and 6 yr, the great majority of nephrotic children have MCNS. The incidence of MCNS is lower in older children. Nevertheless, in many centers including our own, most nephrotic children will be treated with prednisone without a renal biopsy (1). Thus, in our centers, the minimal indications for a renal biopsy in a nephrotic child are either steroid-resistance or steroid-dependence. In other centers, renal biopsy is performed only in children with steroid-resistant nephrotic syndrome (2,3).

STEROID-RESPONSIVE NEPHROTIC SYNDROME

By convention, steroid responsiveness of childhood nephrotic syndrome means the achievement of a total remission (no proteinuria) after no more than 1 month of daily prednisone therapy (60 mg/m², with a maximum daily dose of 80 mg) followed by 1 month of 40 mg/m² every other day (4). In fact, most children who respond to prednisone do so within the first 2 wk of therapy (5). Until recently, there were no data regarding the optimal duration of steroid therapy in
these children. A recent series of controlled trials by the pediatric nephrologists in Germany have greatly clarified this issue. These studies compared three protocols of steroid administration. The "short" course involved the administration of daily prednisone until the urine was protein free for 3 days, followed by alternate-day prednisone therapy until the serum albumin became normal (mean, 16 days). The so-called "standard" protocol was 4 wk of daily prednisone and 4 wk of alternate-day therapy. The "long" course was 6 wk of daily steroids and 6 wk of alternate days. Children who were given a "long course" of daily prednisone to treat the initial episode of nephrotic syndrome had a markedly higher likelihood of remaining in remission than did those who received the "short" or the "standard" courses of daily prednisone. After 1 yr, 81% of those who received the short course had relapsed. The incidence of relapse in the first year was 61% with the standard protocol and only 36% with the long protocol. The outcome of the group that received the long course remained significantly better after 2 yr of follow-up. Interestingly, when either short or standard therapy was given for a recurrence of the nephrotic syndrome, there was no difference in the duration of the remissions (5). Side effects of steroid therapy were comparable in the standard and long therapy groups. Those investigators therefore recommend the use of the long protocol, 6 wk of oral prednisone daily and 6 wk of alternate-day therapy, to treat the initial episode of nephrotic syndrome, but a short course to treat relapses (4).

Most children with steroid-responsive nephrotic syndrome do well, although they may continue to have recurrences of the nephrotic syndrome for many years. In a retrospective series, it has been reported that 14% of patients who develop the nephrotic syndrome before age 6 continue to have relapses as adults (6). Usually, these relapses are well tolerated and can be treated with additional short courses of oral prednisone.

Some steroid-responsive children require high doses of oral steroids to maintain a remission. These steroid-dependent children may develop significant steroid side effects such as growth failure, hypertension, cataracts, or bone disease. In these patients, treatment with an oral alkylating agent, such as cyclophosphamide or chlorambucil, may be appropriate. These drugs are well tolerated acutely (7). Some children will develop mild leukopenia that generally clears when the drug is held for a short period of time. Some families have complained that they notice more hair on the child's comb during a course of treatment with an oral alkylating agent, but noticeable alopecia is rare in these children. The primary concern with these agents centers on possible long-term side effects. First, treatment with alkylating agents has been associated with an increased incidence of tumors. There are no data demonstrating that secondary malignancies occur in children who receive a relatively short course of oral alkylating agent therapy for the nephrotic syndrome. However, the possibility can not be discounted. Second, there is a significant incidence of sterility in children who have been treated with these drugs (8), more commonly in boys than in girls. In some series, the incidence of sterility was as high as 15 to 20%. This complication is dose dependent, and the incidence may be less in recent years because the cumulative dose has been lowered. A significant fraction of steroid-dependent children treated with either cyclophosphamide or chlorambucil have a prolonged and/or permanent remission of their nephrotic syndrome, allowing them to discontinue all therapy. In a collaborative study, also done in Germany, the incidence of prolonged remissions was 67% in children treated with cyclophosphamide for 12 wk compared with 22% in children treated for 8 wk (9). The cumulative dose of cyclophosphamide in the patients treated for 12 wk was 168 mg/kg, which is below the presumed threshold for gonadal toxicity (10). In contrast, Ueda et al. (11) compared 8- and 12-wk courses of cyclophosphamide in children with steroid-dependent nephrotic syndrome and found no difference in remission rate. The explanation for the discrepancy between these two studies is unclear. Recently, there was a multicenter controlled trial comparing chlorambucil and cyclosporine in children with steroid-dependent nephrotic syndrome. The actuarial remission rate after 2 yr was 45% in the chlorambucil-treated group and only 5% after cyclosporine (12).

**STEROID-RESISTANT NEPHROTIC SYNDROME**

A small percentage of children with nephrotic syndrome do not respond to treatment with oral prednisone. A very common biopsy finding in such a child is FSGS. Although these cases are relatively uncommon, FSGS is the most common progressive glomerular disease and the second most common cause of end-stage renal failure in children (13). By itself, alkylating agent therapy has little or no effect in prednisone-resistant FSGS (14).

Over the past 10 yr, we and our colleagues have treated these children with a protocol involving multiple infusions of high-dose intravenous methylprednisolone often in combination with oral alkylating agent therapy (15,16). Because of the difficulty in collecting accurate timed urine collections, we estimated GFR using the formula of Schwartz and his coworkers (17,18). We quantified proteinuria as the ratio of urine protein concentration in milligrams per deciliter to urine creatinine concentration in the same units. This ratio correlated well with the mag-
nitude of proteinuria in carefully collected 24-h urines in our FSGS patients, confirming previous work in other centers (19,20). We interpret a protein/creatinine ratio less than 0.2 as normal. A ratio between 0.2 and 0.5 will be designated minimal, between 0.5 and 2, moderate, and more than 2, nephrotic range proteinuria.

RESULTS OF METHYLPREDNISOLONE PULSE THERAPY

A total of 25 steroid-resistant FSGS patients have been treated and monitored for at least 2 yr. The average age at the start of the protocol was 7.4 yr. Seventeen (68%) of the children were boys; eight (32%) were girls. Five of the 25 had responded to oral prednisone at an earlier time and had then become steroid-resistant. The remaining 20 children were resistant to oral prednisone at the onset of their nephrotic syndrome. The treatment protocol varied slightly within this group. Our current protocol is as follows: during the first 2 wk, the children received a total of six infusions of methylprednisolone. The dose of methylprednisolone throughout the protocol was 30 mg/kg per infusion with a maximum of 1 g. After these 2 wk, the children were restarted on oral prednisone at a dose of 2 mg/kg every other day and this was maintained throughout the remainder of the protocol. For the next 8 wk, the children received weekly infusions of methylprednisolone. If they had improved by this point, the interval between infusions was increased to every 2 wk for a total of four infusions. Patients were then given eight monthly and three semimonthly infusions of methylprednisolone. At this point, the infusions were discontinued and the oral prednisone was tapered to zero.

Many of these children also received alkylating agent therapy. The criteria for the use of alkylating agents were either that nephrotic-range proteinuria persisted after the first 10 wk of methylprednisolone therapy or that there was initial improvement with a subsequent significant increase in proteinuria. In either case, the protocol was restarted and the alkylating agents were given during the 8 wk of weekly methylprednisolone infusions. We used cyclophosphamide (2 mg/kg/day) or chlorambucil (0.2 mg/kg/day) interchangeably at the discretion of the individual physician. Eight of the 25 patients did not receive alkylating agent therapy. Ten patients had one course, four had two courses, and three had more than two courses of this treatment.

The status of these patients at their most recent follow-up is summarized in Table 1. The mean follow-up period is 55 months. Twenty-four of our 25 patients had a normal estimated GFR at their most recent follow-up visit. One child developed chronic renal failure and died at another facility where she was being dialyzed. Fifteen (60%) of the children were in complete remission. Fourteen of these have completed the protocol and were receiving no medication at their last visit. Two children had minimal proteinuria, two had moderate proteinuria, and five remained nephrotic. The remission rate did not vary significantly as a function of the number of courses of alkylating agent therapy. This probably reflects the result of two conflicting forces. The children who received multiple courses of alkylating agents were, by definition, more difficult to treat than were those who did not require this treatment. At the same time, however, as in the milder cases, the children probably benefited from the more intensive therapy. The pretreatment estimated GFR was 137 mL/min/1.73 m² (median, 118; range, 68 to 344), whereas at follow-up, the mean was 129 mL/min/1.73 m² (median, 114; range, 0 to 273). In contrast, there was a dramatic fall in proteinuria. Pretreatment, the mean urinary protein/creatinine ratio was 12.4 (median, 10.3; range, 3.8 to 39.7). At follow-up, the mean was 2.0 (median, 0.15; range, 0 to 15.3) and this difference was statistically significant with a P value of less than 0.001.

The side effects of this protocol were relatively mild considering the large doses of medication given over a long period of time. Nausea was common during the methylprednisolone infusions, particularly when the interval between infusions was 1 month or longer. Five of the children developed small cataracts during their treatment. These had no effect on their vision. In one child, the cataracts disappeared when he went into remission and treatment was discontinued. Five children had slowing in their growth rate during the protocol. One of these children had catch-up growth when she went into remission and was taken off therapy. The remaining four children are of short stature. Five children developed hypertension during the protocol. This was easily managed with antihypertensive therapy and resolved when the methylprednisolone was discontinued. Three of the 17 children who received at least one course of alkylating agent therapy developed leukopenia, which resolved when the drug was discontinued. Each child

<table>
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<tr>
<th>TABLE 1. Current status of FSGS patients treated with pulse methylprednisolone protocola</th>
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<tr>
<td>Remission</td>
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<td>Minimal Proteinuria</td>
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<td>Moderate Proteinuria</td>
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<td>Nephrotic Proteinuria</td>
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a Patients in remission had a normal estimated GFR and a protein/creatinine ratio (P/Cr) less than 0.2 on a random urine collection. Patients with minimal proteinuria have a normal GFR and a P/Cr between 0.2 and 0.5. Patients with moderate proteinuria have a normal GFR and a P/Cr between 0.5 and 2.0. Patients with nephrotic proteinuria have a normal GFR and a P/Cr of more than 2.0.
was able to complete the full 8 wk of alkylating agent therapy.

The pulse methylprednisolone therapy appeared to improve the overall course of the disease. The incidence of hospitalizations for complications of the disease or its treatment was very low. For example, we rarely had to hospitalize a patient for the treatment of refractory edema or serious infection. Before this protocol was started, such admissions were very common in children with prednisone-resistant nephrotic syndrome.

This was an uncontrolled study, and the extent to which our patients can be compared with previous series of children with FSGS is unclear. For this reason, we have not done statistical comparisons with the other series. The remission rate in other series of children with FSGS was 0 to 20% (21-24). The incidence of ESRD or death in these patients has been reported as 21 to 75% (21-27). A number of our patients have been in remission and off treatment for many years. We have not seen late recurrences of the nephrotic syndrome in this long-term follow-up group, although a very few in our overall experience have relapsed and then responded to steroid therapy (one required pulse therapy).

We found that pulse therapy with iv methylprednisolone caused a rapid and sustained decrease in the magnitude of the proteinuria in children with steroid-resistant nephrotic syndrome and FSGS. In our initial series, proteinuria decreased from 247 to 96 mg/m²/h. Treatment of FSGS with methylprednisolone, often in conjunction with oral alkylating agents, appears to increase the incidence of long-term remission and decrease the incidence of ESRD or death. Side effects are acceptable. We hope to undertake a multicenter, controlled trial of this protocol.

OTHER THERAPIES

There has been considerable recent study of the use of cyclosporine and angiotensin-converting enzyme inhibitors in the treatment of children with different forms of the nephrotic syndrome. Children with steroid-responsive nephrotic syndrome tend to respond to treatment with oral cyclosporine much as they do with prednisone. Niaudet and Broyer reported that 39 of the 44 patients with steroid-responsive nephrotic syndrome responded to treatment with cyclosporine (28). In most cases, however, the patients relapsed soon after the cyclosporine was withdrawn. The picture is less encouraging in children with steroid-resistant nephrotic syndrome. In the same review, only 10 of the 38 patients responded to cyclosporine. In those who did respond, the duration of the remission was variable. In some cases, the remission persisted after the drug was discontinued. Overall, most children with MCNS responded to cyclosporine whereas only 35% of patients with FSGS went into remission. Similar results were reported by Melocoton et al. (29), who found that seven of eight patients with steroid-dependent nephrotic syndrome achieved a remission with cyclosporine treatment. In contrast, only 1 of 10 children with steroid-resistant nephrotic syndrome achieved a complete remission. Recently, Niaudet et al. reported a group of 31 children with steroid-resistant nephrotic syndrome, of whom 19 had MCNS and 12 had FSGS (30). Those children were treated for 6 months with both cyclosporine and oral prednisone. Fourteen (45%) went into remission, 3 had a partial response, and 14 did not respond. One child with FSGS went into end-stage renal failure after 2 months of this treatment. This was a preliminary report with no long-term follow-up (30). The side effects of cyclosporine are significant. In the review mentioned earlier (28), 26 of 83 children had a rise in serum creatinine during cyclosporine therapy. In seven of these, renal function did not return to normal when the drug was stopped. It is difficult to know whether this deterioration was a result of their basic disease or of irreversible nephrotoxicity (28,31,32). There have also been reports of histologic nephrotoxicity in a small number of nephrotic children (29,33). In addition, the reported incidence of hypertension in nephrotic children treated with cyclosporine has been as high as 39%.

There have been several studies on the use of angiotensin-converting enzyme inhibitors in children with steroid-resistant nephrotic syndrome. Milner and Morgenstern reported the treatment of six such children with enalapril (34). Proteinuria was decreased significantly, with a fall in the urine protein/creatinine ratio from 29 to 10. Serum albumin did not change, however.

SUMMARY

Children with steroid-responsive nephrotic syndrome generally do well, although the disease can be very protracted with multiple relapses and, occasionally, with acquired steroid-resistance. The experience in Germany suggests that the incidence of long-term initial remissions may be increased by increasing the length of initial steroid therapy to 6 wk of daily prednisone followed by 6 wk of alternate-day therapy. In a small number of cases, alkylating agent therapy is necessary in these patients. In children with FSGS, it appears that the methylprednisolone protocol improves the prognosis, although we feel strongly that this should be confirmed by a multicenter trial. An important clinical benefit of cyclosporine or angiotensin-converting enzyme inhibitors in the
treatment of children with nephrotic syndrome has not been demonstrated.

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REFERENCES


