Abstract. The ability to predict the course in children with newly diagnosed minimal change nephrotic syndrome (MCNS) may have significant therapeutic implications. Previous attempts based on data available at disease onset have not been successful. Therefore, it was investigated whether characterization of the initial response to adrenocortical steroids and the course during the early months of disease are predictive of the subsequent outcome. Three hundred-eighty-nine children with MCNS, diagnosed at onset, were treated with standard prednisone regimens and monitored for up to 17 yr (mean, 9.4 yr). They were classified, after 8 wk of therapy, as initial responders (complete remission) or initial nonresponders (continued proteinuria). Subsequent classifications included nonrelapsers, infrequent relapsers, and frequent relapsers. At 8 yr of follow-up, 80% of patients were in remission. Three-fourths of initial responders who remained in remission during the first 6-month period after initial therapy (nonrelapsers; 40% of the entire series) either continued in remission during their entire course or relapsed rarely. In contrast, initial relapsers, both frequent and infrequent, achieved a nonrelapsing course only after an average of 3 yr. Unremitting proteinuria during the initial 8 wk of treatment was followed by progression to ESRD in 21%. When proteinuria during the initial 8 wk continued through the subsequent 6 months, progression to renal failure occurred for 35%. Although 95% of children with MCNS do well, 4 to 5% die from complications or undergo progression to ESRD. Documentation of the early course aids in identifying those at increased risk for a poor outcome. More aggressive therapy may be indicated for these individuals. (J Am Soc Nephrol 8: 769–776, 1997)

In 1967, the International Study of Kidney Disease in Children (ISKDC) began a multicenter prospective study of childhood nephrotic syndrome, to determine clinical and laboratory characteristics and to conduct a series of controlled therapeutic trials (1–7). This report characterizes the long-term course and outcome of minimal change nephrotic syndrome (MCNS), with the demonstration that the pattern of steroid responsiveness during the first 6 months predicts the subsequent pattern of response and relapse.

Materials and Methods

Patients
Between January 1967 and April 1976, 521 children with recent-onset nephrotic syndrome were entered into a prospective study that involved 19 participating centers in 12 countries in North America, Europe, and Asia. Written informed consent was obtained from all participants. Criteria for admission were (1) heavy proteinuria, of ≥40 mg/bm2 BSA (≥0.96 g/day-m2), determined with an overnight collection; (2) hypoalbuminemia, of ≤2.5 g/dL (≤25 g/L); (3) age of >12 wk and <16 yr; (4) no prior treatment with steroids or other cytotoxic or immunosuppressive agents; and (5) no evidence of underlying systemic disease or exposure to agents known to be associated with the nephrotic syndrome.

All patients underwent renal biopsy after entry into the study, before initiation of therapy. Of the 521 patients, 389 (74.7%) were diagnosed histopathologically by the ISKDC central pathologists as having MCNS. This is in striking contrast to the experience with adults, among whom membranous glomerulonephritis (a rare disease among children) predominates.

Prednisone Regimens
The initial treatment was 60 mg/24 hr-m2 prednisone (maximum daily dosage, 80 mg/24 hr-m2) in three divided daily doses for 4 wk, followed by 40 mg/24 hr-m2 (maximum daily dosage, 60 mg/24 hr-m2) in divided doses on 3 consecutive days of 7 for 4 wk. The treatment of relapse was 60 mg/24 hr-m2 in divided doses until response (maximum of 4 wk), followed by 40 mg/24 hr-m2 in divided doses on 3 consecutive days of 7 for 4 wk.

Response was defined as a reduction in the rate of urinary excretion of protein to <4 g/hr-m2 (Albustix, 0 to trace) for 3 consecutive days. Relapse involved a reappearance of proteinuria of ≥40 mg/hr-m2 (Albustix, ++ or greater) for 3 consecutive days. Initial responders were patients who responded during the 8 wk of the initial prednisone regimen. Initial nonresponders were patients who failed to respond during the initial 8 wk of prednisone therapy.

Some of the patients subsequently were entered into therapeutic
Analysis of Clinical Courses

For the purpose of analysis, the courses of the patients were divided into three phases, as follows: (1) the initial 8 wk after entrance into the study; (2) the 6-month period after initial therapy; and (3) the subsequent course, classified annually on the basis of data reported during each 1 yr of follow-up (Tables 1 and 2).

For assessing the status of patients over time, a period of 2 consecutive yr with the same classification was required to characterize the course of the patients and to identify clinically significant changes. This allowed transient changes in the frequency of relapses to be disregarded.

Histopathology

Renal tissue was processed, evaluated, and classified into histologic subgroups as previously described (2,9). Because there were no correlations between histologic subtypes of MCNS and the long-term clinical course, data for all patients were pooled for the present analysis.

Statistical Methods

The data were evaluated for categorical measures using proportions and for quantitative measures using means and SD. The 95% confidence limits were estimated to describe response times and to assess differences between patient subgroups (10). Patients were evaluated at irregular intervals during the follow-up period. Annual assessments were obtained for all patients, and the clinical courses were classified according to the criteria listed in Table 2. Analysis of the subsequent courses was based on the proportion of patient reports in each annual classification.

Table 1. Initial and 6-month classifications

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>% of Total</th>
<th>% of Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial responder: attainment of complete remission</td>
<td>334</td>
<td>92%</td>
<td>334</td>
</tr>
<tr>
<td>Course during subsequent 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial nonresponder: no relapse</td>
<td>148</td>
<td>45.2</td>
<td>45.2</td>
</tr>
<tr>
<td>initial infrequent relapser: one relapse</td>
<td>73</td>
<td>21.9</td>
<td>21.9</td>
</tr>
<tr>
<td>initial frequent relapser: two or more relapses</td>
<td>102</td>
<td>30.6</td>
<td>30.6</td>
</tr>
<tr>
<td>subsequent nonresponder: proteinuria for ≥8 weeks</td>
<td>11</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Initial nonresponder: continuous proteinuria during the initial 8 weeks of therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Course during subsequent 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>continued nonresponder: unremitting proteinuria</td>
<td>17</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>subsequent responder: loss of proteinuria</td>
<td>12</td>
<td>3.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Table 2. Annual classifications

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>% of Total</th>
<th>% of Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonrelaper: no relapse</td>
<td>148</td>
<td>45.2</td>
<td>45.2</td>
</tr>
<tr>
<td>Infrequent relapser: one to three relapses</td>
<td>73</td>
<td>21.9</td>
<td>21.9</td>
</tr>
<tr>
<td>Frequent relapser: four or more relapses</td>
<td>102</td>
<td>30.6</td>
<td>30.6</td>
</tr>
<tr>
<td>Nonresponder followed by remission: 8 weeks of proteinuria followed by remission</td>
<td>11</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Nonresponder not followed by remission: unremitting proteinuria</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

Characteristics at Onset

The 389 patients with MCNS included 66% male patients and 34% female patients. Age at onset was 4.8 ± 2.9 yr (mean ± SD). Age at entry was 4.9 ± 2.9 yr, with a range of 0.87 to 14.8. A figure showing the age distribution at onset has been published (4). As previously reported (4), baseline clinical and laboratory data did not correlate with renal histopathologic findings, response to therapy, or subsequent course and, therefore, are not reported here. Similarly, no correlations were found with microscopic hematuria, which was present at onset in one-third of patients.

Geographic Distribution

The series included 47.8% patients from Europe, 16.5% from Japan and Hong Kong, and 35.7% from North America. Histopathologic subtypes and the 6-month classifications did not differ among these groups.

Course

Follow-up times averaged 113 ± 62 months, with a maximum of 211 months (17.6 yr). Follow-up monitoring included 341 patients at 2 yr from entry, 301 at 5 yr, 262 at 7 yr, 223 at 10 yr, 186 at 12 yr, and 60 at 15 yr.

Six-month classification was possible for 363 of the 389 children (93%) (Table 3). For 13 patients, there were insufficient data to characterize the courses during the first 6 months; for 13 patients, there were no follow-up data beyond entrance. Of the 363 patients, 334 (92%) were initial responders and 29 (8%) were initial nonresponders (Table 3). Neither GFR at onset nor GFR at last follow-up examination correlated with

Table 3. Six-month classifications

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>% of Total</th>
<th>% of Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial responder (334, 92%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonresponder</td>
<td>148</td>
<td>45.2</td>
<td>45.2</td>
</tr>
<tr>
<td>infrequent relapser</td>
<td>73</td>
<td>21.9</td>
<td>21.9</td>
</tr>
<tr>
<td>frequent relapser</td>
<td>102</td>
<td>30.6</td>
<td>30.6</td>
</tr>
<tr>
<td>subsequent nonresponder</td>
<td>11</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Initial nonresponder (29, 8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with continued nonresponse</td>
<td>17</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>with subsequent response</td>
<td>12</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Total</td>
<td>363</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
classification at 6 months or with histopathologic findings, except for initial nonresponders, who remained nonresponsive throughout their courses (see below).

Of the 148 initial nonrelapsers, 16% sustained a nonrelapsing pattern throughout their entire course and 60% relapsed rarely, i.e., no 2-yr period with at least one relapse each year (Figure 1). Only six initial nonrelapsers became frequent relapsers, and half of their subsequent annual assessments were as nonrelapsers.

Among the 73 initial infrequent relapsers, 70% became nonrelapsers within 0.3 to 7.7 yr (median, 2.7 yr) (Figure 2). Only seven initial infrequent relapsers (9.6%) were subsequently classified as frequent relapsers.

Of the 102 initial frequent relapsers, 63% became nonrelapsers within an average period of 3 yr; and an additional 34% of initial frequent relapsers became infrequent relapsers within 2 yr (Figure 3). There was no significant difference in time to nonrelapse or infrequent relapse among those who received prednisone, azathioprine, or cyclophosphamide, singly or in combination. Thus, although cyclophosphamide plus prednisone improved the early course for frequent relapsers, compared with prednisone alone (1), all of these patients did equally well with long-term monitoring.

The pattern of response for the entire group is shown in Figure 4. It can be seen that the proportion of nonrelapsers gradually increased, reaching approximately 80% by 8 yr. Nevertheless, 5 to 10% of patients continued to relapse at the time of last follow-up examination, although very few were frequent relapsers.

Fifteen patients who were initially steroid-responsive became transiently nonresponsive (i.e., over a period of at least 8 wk) during the latter years of follow-up monitoring. The 6-month classification of these patients consisted of two nonrelapsers, three infrequent relapsers, two frequent relapsers, and eight subsequent nonresponders. In addition to prednisone, seven were treated with cyclophosphamide, one with azathioprine, and three with both of these drugs; four received prednisone alone. None became persistently nonresponsive, except for one frequent relapser who remained steroid-responsive for 8 yr but ultimately became steroid-nonresponsive and experienced renal failure.

Twenty-nine patients were initial nonresponders (Table 3). For 12 of them (3.3% of total), the proteinuria was resolved within the subsequent 6 months. Treatment of these 12 patients after the initial 8 wk of prednisone administration included prednisone alone (one patient), prednisone plus azathioprine (two patients), prednisone plus cyclophosphamide (eight patients), and all three drugs (one patient). It was not possible to determine whether their remissions resulted from continued therapy or were spontaneous. However, no beneficial effect was observed among nonresponders in the trial of azathioprine (7). In the trial of cyclophosphamide (1), proteinuria subsided...
Subsequent Annual Classifications:

- No Relapse: 34%
- Infreq Relapse: 28%
- Freq Relapse: 32%

Subsequent Annual Classifications:

- No Relapse: 21%
- Infreq Relapse: 57%
- Freq Relapse: 8%
- Transient Non-Response: 2%
- Intermittent Proteinuria: 12%

Subsequent Annual Classifications:

- No Relapse: 90%
- Infreq Relapse: 5%
- Transient Non-Response: 3%
- Intermittent Proteinuria: 2%

Figure 2. Subsequent classification of 73 patients who were infrequent relapsers at 6 months. The classification for 70% was as a nonrelapser, and a similar percentage of the following annual classifications was as a nonrelapser. The subsequent classifications of infrequent and frequent relapsers are shown in tabular form. Intermittent proteinuria reflects transient proteinuria less than that required to define a relapse.

Earlier among patients who received cyclophosphamide, compared with those who received prednisone alone, but the proportions of patients for whom the proteinuria was resolved were similar in the two treatment groups. Among these 12 patients, one with nil disease died of sepsis 7 months after onset (11). Seven became nonrelapsers within 2.3 yr of entry. One other became an infrequent relapser at 3 yr, and three became frequent relapsers within 0.6 to 3.9 yr (median, 1.5 yr). The 11 surviving patients were nonrelapsers for 69% of the follow-up time of 6 to 13 yr. The distribution of histopathologic findings did not differ from that of the remainder of the series, and none of these patients developed ESRD.

Seventeen patients (4.7% of total) were initial and continued nonresponders. Their age and gender distributions were similar to those of the entire study population. Ten of them responded subsequently, within 0.5 to 3.6 yr from entrance into the trial (median, 0.8 yr), and did well, with follow-up periods of 2 to 16 yr. Their treatment included prednisone alone (one patient), prednisone plus azathioprine (four patients), prednisone plus cyclophosphamide (two patients), and all three drugs (three patients). Again, it was not possible to relate their ultimate remissions to any particular form of therapy. The histopathologic classifications included nil disease (three patients), mild mesangial thickening (one patient), mild mesangial hyperplasia (three patients), and focal glomerular obsolescence (three patients).

The remaining seven initial and continued nonresponders (Table 4) included one who died from pneumococcal peritonitis within 6 months of entrance into the study. The other six developed ESRD. One of them responded to prednisone from time to time but ultimately returned to a nonresponder state and experienced ESRD by year 9 of follow-up monitoring. The other five maintained nonresponsive courses throughout. Half of the patients received cyclophosphamide, and half received prednisone alone.

Follow-up biopsies were performed at the discretion of the patients' physicians and were available for only 65 patients. Compared with the baseline readings, the classifications of the follow-up biopsies, performed by the ISKDC pathologists, were discordant for 19 (29%). For 13 the biopsy diagnosis changed to focal glomerulosclerosis. Nine of the 13 continued to do well, whereas the other four (see above) developed ESRD. The four patients who developed ESRD and had follow-up biopsies showed focal global glomerulosclerosis or focal segmental glomerulosclerosis (FSGS); one of them later developed proliferative glomerulonephritis (Table 4).

Discussion

Among the difficult tasks facing clinicians treating children with MCNS are predicting both the initial and subsequent courses and determining the prognosis. These evaluations are
used in counseling parents and in making therapeutic decisions.

The goals of the ISKDC were to conduct controlled clinical therapeutic trials and to identify early clinical characteristics that predict the long-term course. As previously reported, few clinical characteristics correlated with histopathologic characteristics and outcome, except that initial steroid-responsiveness predicted MCNS with a high degree of accuracy (3,4). Steroid-nonresponsiveness was histopathologically nonspecific but indicated glomerular diseases with poorer outcomes than that with MCNS. Undetermined in the initial studies were the indicators of long-term outcome with MCNS.

The current report is based on the only large prospective study of an unselected, previously untreated series of children with recent-onset MCNS and renal biopsy at entry. Because renal biopsies are no longer routinely performed for children thought to have MCNS (or, in operational terms, who have steroid-responsive disease), it is unlikely that such a study will ever be duplicated.

On the basis of preliminary data (3), patients were classified according to their course during the 6 months after the initial 8-wk period of therapy. Because of the variability in the patterns of relapses, a method was devised to characterize the subsequent courses. This approach was designed to ignore transient changes and to base the long-term analyses on a response/relapse pattern (nonrelapsing, infrequent relapsing, etc.) that persisted during a period of at least 2 consecutive yr. The approach was validated by the finding that those who were nonrelapsers for 2 consecutive yr continued their nonrelapsing courses more than 86% of the time, regardless of their 6-month classification. In contrast, those who were frequent relapsers for 2 consecutive yr were nonrelapsers only 34 to 47% of the time. Patients thus can be reassured that a nonrelapsing course for 2 consecutive yr augurs an excellent prognosis, in agreement with the observation of Habib et al. (12,13). This is in contrast to the findings of Lewis et al. (14), who concluded that a 4-yr period was required to be predictive of a subsequent nonrelapsing course.

These analyses confirmed an early impression (3) that the 6-month classification is highly predictive of the subsequent course. Three-fourths of initial responders who remained in remission during the subsequent 6-month period (40% of the entire series) either continued in remission throughout their entire course or relapsed rarely. Thus, this early nonrelapsing pattern augurs an excellent prognosis for approximately one-third of children with MCNS.

In contrast, initial relapsers achieved a nonrelapsing course only after an average of 3 yr. The frequency of subsequent relapses and the length of time to achieve a nonrelapsing state did not differ between initial infrequent and frequent relapsers, in contrast to the impression one gathers from the literature. The failure to find such a difference cannot be explained by the treatment of frequent relapsers with drugs other than prednisone, because the time frame for frequent relapsers to become infrequent relapsers or nonrelapsers did not correlate with the drug regimen used.

The 80% remission rate at 8 yr (Figure 4) is somewhat better than that reported in other series, ranging from 66% at 9 yr to 95% at 15 to 20 yr (12,15–17). This might be explained by the enrollment of patients before biopsy or treatment, avoiding the bias of selected referral of patients with disease that is difficult to manage.

Most patients who fail to respond to an initial course of prednisone ultimately attain a full remission, independent of the treatment regimen. Nevertheless, an initially nonresponsive state greatly increases the risk of poor outcome. Despite the small number of initial nonresponders, unremitting proteinuria during the initial 8 wk of prednisone therapy was followed by progression to ESRD in 21%. In addition, 9 of the 10 deaths occurred in patients who were initially nonresponsive to prednisone or who relapsed during the first 8-wk period of therapy. One-third of 17 patients who had unremitting proteinuria during the initial 8 wk of therapy and the subsequent 6 months progressed to renal failure, making this an even more ominous predictor of outcome.

As reported in 1984, a total of 10 patients in this series died within 2 yr of disease onset (11), including four of the patients reported here. Nine of the 10 responded initially only briefly or not at all. The additional follow-up monitoring confirms the earlier observation that early nonresponse marks a group of
Figure 4. Annual classification of patients according to response category, demonstrating the progressive decline in the infrequent and frequently relapsing categories.

Table 4. Clinical data and course for the seven initial and continued nonresponders who developed ESRD or died

<table>
<thead>
<tr>
<th>Age at Onset (yr)</th>
<th>Gender</th>
<th>Annual Classification</th>
<th>Initial Pathology&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Follow-up Pathology/Year&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total Years of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6</td>
<td>M</td>
<td>Never responded</td>
<td>FGO</td>
<td>FGGS/0.25, FSGS/1, MCGN/5, DPGN/5</td>
<td>8</td>
</tr>
<tr>
<td>1.6</td>
<td>F</td>
<td>Occasional responses</td>
<td>FTC</td>
<td>FTC</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>followed by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>nonresponsive course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td>F</td>
<td>Never responded; died&lt;sup&gt;b&lt;/sup&gt;</td>
<td>FTC</td>
<td>FTC</td>
<td>2</td>
</tr>
<tr>
<td>14.6</td>
<td>M</td>
<td>Never responded; died&lt;sup&gt;b&lt;/sup&gt;</td>
<td>FTC</td>
<td>FTC</td>
<td>1.4</td>
</tr>
<tr>
<td>5.6</td>
<td>F</td>
<td>Never responded</td>
<td>NIL</td>
<td>FSGS/3</td>
<td>3</td>
</tr>
<tr>
<td>2.6</td>
<td>M</td>
<td>Never responded</td>
<td>FGO</td>
<td>FGGS with tubular atrophy/3</td>
<td>8</td>
</tr>
<tr>
<td>3.0</td>
<td>M</td>
<td>Never responded; died from pneumococcal peritonitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NIL</td>
<td></td>
<td>0.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> NIL, nil disease; FGO, focal glomerular obsolescence; FTC, focal tubular changes; FGGS, focal global glomerulosclerosis; MCGN, mesangiocapillary glomerulonephritis; DPGN, diffuse proliferative glomerulonephritis.

<sup>b</sup> See reference 11.

patients at risk of early death. The death rate of 2.5% reported here is on the low end of the range of 2.5 to 6.7% reported by others, whereas the renal failure rate is within the 0 to 3.5% reported in other studies (12,14–16,18).

Although this study did not address the relationship between MCNS and FSGS, the finding of focal glomerular lesions in 13 (20%) of 65 second biopsies may reflect the operation of common pathogenetic mechanisms in the development of these two histopathologic patterns (19–22). FSGS in nephrotic children is not uniform in histopathologic severity or clinical onset, course, and responsiveness to steroid therapy, and some of the differences may relate to the variable severity of glomerular...
injury (20). Approximately 30% of nephrotic children with initial FSGS respond to steroid therapy, and most of them continue to do well (19). Nine (69%) of 13 children with late FSGS and global glomerulosclerosis, after initial MCNS, did well. These glomerular lesions may represent a continuum rather than separate disease entities.

Careful documentation of the early course of patients with MCNS can help in identifying those at highest risk of a poor outcome, namely initial nonresponders. Close observation of these patients is needed and more intensive therapy may be warranted for patients who are initial and continued nonresponders at 6 months, because more than one-third of them may eventually develop ESRD. Such therapy might involve the use of cyclophosphamide, cyclosporin, or other therapies. Cyclophosphamide was found to induce remission in several uncontrolled and two controlled studies (1,16,23-26), but the ISKDC trial (1), comparing this drug with prednisone, showed that cyclophosphamide only shortened the time to response and did not change the proportion of responders. Cyclosporin has shown some efficacy in uncontrolled studies (17,26-30). In two reports, Niaudet and co-workers (27,28) reported complete remission in five of eight patients and five of six patients treated with cyclosporin and prednisone, but not with cyclosporin alone. The Collaborative Group of the French Society of Nephrology (30), studying adults, reported remission in 14 of 21 patients with steroid-resistant MCNS (30). Although there is no universally accepted form of therapy for this group of patients, the observations suggest that these two drugs may be of benefit.

In conclusion, 95% of children with MCNS do well, with as many as one-third maintaining a nonrelapsing or rarely relapsing state throughout their entire course. Despite these overall excellent outcomes, 4 to 5% of patients may die from complications or progress to ESRD.

Acknowledgments
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