AJKD
Original Investigation

The Clinical Course of Minimal Change Nephrotic Syndrome With Onset in Adulthood or Late Adolescence: A Case Series

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Background: Few studies have examined the treatment and outcome of adult-onset minimal change nephrotic syndrome (MCNS). We retrospectively studied 125 patients who had MCNS with onset in either adulthood or late adolescence. Presenting characteristics, duration of initial treatment and response to treatment, relapse patterns, complications, and long-term outcome were studied.

Study Design: Case series.

Setting & Participants: Patients with new-onset nephrotic syndrome 16 years or older and a histologic diagnosis of MCNS in 1985 to 2011 were identified from pathology records of 10 participating centers.

Outcomes: Partial and complete remission, treatment resistance, relapse, complications, renal survival.

Results: Corticosteroids were given as initial treatment in 105 (84%) patients. After 16 weeks of corticosteroid treatment, 92 (88%) of these patients had reached remission. Median time to remission was 4 (IQR, 2-7) weeks. 7 (6%) patients initially received cyclophosphamide with or without corticosteroids, and all attained remission after a median of 4 (IQR, 3-11) weeks. 13 (10%) patients reached remission without immunosuppressive treatment. One or more relapses were observed in 57 (54%) patients who received initial corticosteroid treatment. Second-line cyclophosphamide resulted in stable remission in 57% of patients with relapsing MCNS. Acute kidney injury was observed in 50 (40%) patients. Recovery of kidney function occurred almost without exception. Arterial or venous thrombosis occurred in 11 (9%) patients. At the last follow-up, 113 (90%) patients were in remission and had preserved kidney function. 3 patients with steroid-resistant MCNS progressed to end-stage renal disease, which was associated with focal segmental glomerulosclerosis lesions on repeat biopsy.

Limitations: Retrospective design, variable treatment protocols.

Conclusions: The large majority of patients who had MCNS with onset in adulthood or late adolescence were treated with corticosteroids and reached remission, but many had relapses. Cyclophosphamide resulted in stable remission in many patients with relapses. Significant morbidity was observed due to acute kidney injury and other complications. Progression to end-stage renal disease occurred in a few patients and was explained by focal segmental glomerulosclerosis.

Am J Kidney Dis. 69(5):637-646. © *2016 by the National Kidney Foundation, Inc.*

INDEX WORDS: Corticosteroids; cyclophosphamide; minimal change disease (MCD); nephrotic syndrome (NS); immunosuppression; adult-onset MCNS; adults; adolescents; partial remission; complete remission; treatment resistance; relapse; renal survival; acute kidney injury (AKI); case series.

Minimal change nephrotic syndrome (MCNS) is the most frequent cause of nephrotic syndrome in children.[1] In adults, MCNS accounts for 15% to 20% of patients with nephrotic syndrome.[2] There is no evidence from randomized controlled trials to support the efficacy of any treatment modality in adults with MCNS.[3] Based on extrapolation from randomized studies in children and observational studies in adults, corticosteroids are the cornerstone of therapy (reviewed in[4]). However, adults differ from

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Received April 15, 2016. Accepted in revised form October 24, 2016. Oirignally published online January 14, 2017.

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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.10.032

children in being less responsive to corticosteroids and more likely to present with acute kidney injury (AKI).[5-9]

In the present study, we retrospectively reviewed 125 patients who had MCNS with onset in adulthood or late adolescence treated in 10 Dutch hospitals. Specific questions relate to: (1) response to initial corticosteroid therapy, and specifically the relationship between dose and duration of initial steroid treatment and (time to) relapse; (2) prevalence and factors associated with spontaneous remissions that we have frequently observed; (3) disease course and response to second-line treatment in patients with relapsing MCNS; (4) the course, severity, and outcome of AKI; (5) other disease- and treatment-related complications; and (6) long-term outcome.

METHODS

Study Design and Patient Selection

From the pathology registries, we identified all adult and older adolescent patients (aged ≥ 16 years at biopsy) diagnosed with minimal change disease January 1, 1985, to September 1, 2011, at Radboud University Medical Center and 9 participating regional hospitals. We reviewed the complete pathology reports. Histologic criteria for MCNS included normal-appearing glomeruli on light microscopy and absence of detectable immunofluorescence staining for immunoglobulin A (IgA), IgG, IgM, C1q, C3, and κ and λ light chains. Exclusion criteria were absence of nephrotic syndrome and MCNS that may have been causally related to an underlying neoplasm, drug, or infection as reported in the literature (Table S1, available as online supplementary material).[10]

Medical records were reviewed for clinical data from presentation until last follow-up. Demographics; presenting characteristics; laboratory parameters; dosage, duration, and response to medical treatments; relapses; and adverse events were recorded. All patients with follow-up of at least 6 months were included, as well as patients who died within 6 months. The study was conducted according to the Code of Conduct for Medical Research. According to local and national policies, ethics approval is not applicable for research with patient files. Chart review was performed under the supervision of physicians who had been involved in the treatment of patients. All data were anonymized, and per applicable regulations for such data, informed consent was not obtained from individual patients.

Definitions

Nephrotic syndrome was defined as proteinuria with protein excretion ≥ 3.5 g/24 hours and serum albumin concentration ≤ 3.0 g/dL. A case of MCNS was defined by diagnosis of nephrotic syndrome and a kidney biopsy specimen showing normal glomeruli on light microscopy and no deposits on immunofluorescence. Complete remission was defined as proteinuria with protein excretion < 0.3 g/24 h or <0.3 g/g creatinine, with progressively increasing serum albumin levels. Partial remission was defined as reduction of proteinuria to protein excretion of 0.3 to 3.5 g/24 h or 0.3 to 3.5 g/g creatinine with a stable serum creatinine level (≤25% increase from baseline) and a decrease > 50% from baseline. Relapse was defined as an increase in urinary protein excretion to ≥3.5 g/24 h or ≥3.5 g/g creatinine in patients who had at least attained a partial remission. Time to remission was calculated from initiation of immunosuppressive therapy to the first day on which remission was observed, and from biopsy in patients who did not receive immunosuppressive therapy. Frequent relapse was defined as 2 or more relapses within 6 months. Steroid dependence was defined as 2 relapses during corticosteroid treatment or within 2 weeks after completing corticosteroid treatment. Corticosteroid resistance was defined as failure to attain either partial or complete remission after 16 weeks of corticosteroid therapy.

Estimated glomerular filtration rate (eGFR) was calculated with the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[11] AKI was defined according to the RIFLE ("risk, injury, failure, loss, end-stage renal disease") criteria.[12] Creatinine level and eGFR before the onset of nephrotic syndrome were usually not available. In order to generate baseline levels, we chose the highest of either eGFR at presentation or the fifth percentile of age- and sex-based reference values.[13] Hypertension was defined as 2 repeated systolic blood pressure measurements ≥ 140 mm Hg or 2 diastolic blood pressure measurements ≥ 90 mm Hg or use of blood pressure−lowering agents.[14]

Treatment

Spontaneous remissions may occur in adult-onset MCNS.[15,16] Therefore, some patients with acceptable symptoms were followed up initially without immunosuppressive treatment. Corticosteroid dose and treatment duration were variable. Initial high-dose corticosteroid treatment usually consisted of prednisone at a dose of ∼1 mg/kg daily with a maximum of 80 mg or 2 mg/kg on alternate days with a maximum of 125 mg. Tapering was based on improvement of symptoms and proteinuria. In general, initial high-dose prednisone treatment was maintained until remission and slowly tapered, with total treatment duration usually lasting 6 months or longer, depending on drug tolerance and individual experience (see Results).

Statistical Analyses

Continuous variables are expressed as mean ± standard deviation or median and range or interquartile range (IQR) when appropriate. For comparison between groups, Mann-Whitney *U* test was used for continuous data and Fisher exact test was used for categorical data.

The Kaplan-Meier method and log-rank test were used for description and comparison of time to remission and time to relapse. $P < 0.05$ was considered statistically significant.

RESULTS

Participants

From the pathology reports, we identified 180 patients 16 years or older diagnosed with minimal change disease in 1985 to 2011. Five patients were excluded because they had childhood onset of nephrotic syndrome, and biopsy confirmation was performed in late adolescence or adulthood because of relapsing disease. Twenty-one patients did not have nephrotic syndrome, and 2 patients had an associated malignant disorder (lymphoma). Twenty-seven patients had insufficient follow-up data. Baseline characteristics of patients with insufficient follow-up were not significantly different from those of patients who were included in the study. In the final analysis, we therefore included 125 patients 16 years or older with MCNS. On kidney biopsy, the median number of glomeruli was 13 (range, 5-40). In 74 (59%) of the included patients, electron microscopic studies were performed, which invariably showed diffuse effacement of podocyte foot

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