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Original Investigation

Long-term Outcome of Biopsy-Proven Minimal Change Nephropathy in Chinese Adults

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Background: Minimal change nephropathy is a common cause of primary nephrotic syndrome in adults. However, there are few studies of its clinical course, response to treatment, and long-term outcome.

Study Design: Retrospective cohort study.

Setting & Participants: 340 consecutive adult patients with nephrotic syndrome and biopsy-proven minimal change nephropathy treated in a university hospital from 1984 until 2004.

Factors: Treatment response groups: primary steroid resistance, frequent relapse (≥4 relapses within 1 year), infrequent relapse (≥1 relapse but not frequent relapse), and no relapse (reference group); disease pattern.

Outcome: Medical problems after diagnosis; patient survival; renal survival.

Results: Median time to remission was 10 (IQR, 8-12) weeks; 179 (52.6%) had no relapse, 42 (12.4%) had infrequent relapses, 86 (25.3%) were frequent relapsers or steroid dependent, and 33 (9.7%) had primary steroid resistance. After a median follow-up of 174.7 (IQR, 119.7-235.0) months, 32 patients developed end-stage renal disease and 62 died (25 after progression to end-stage renal disease). Cox regression analysis showed that age and treatment response groups were the independent predictors of patient survival. Compared to the no-relapse group, the infrequent-relapse group had significantly better patient survival (adjusted HR, 0.19; 95% CI, 0.08-0.44; $P < 0.001$), whereas the primary-steroid-resistance group had significantly worse patient survival (adjusted HR, 5.87; 95% CI, 1.83-18.85; $P < 0.001$). Renal survival was excellent except in the primary-steroid-resistance group.

Limitations: Retrospective study.

Conclusions: A substantial proportion of adult patients with minimal change nephropathy continue to have disease flares more than 10 years after the initial presentation, and medical problems after diagnosis are common.

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INDEX WORDS: Minimal change nephropathy (MCN); adult onset; steroid resistant; relapse, disease flare, remission, glomerulonephritis; nephrotic syndrome; glucocorticoid; renal survival; end-stage renal disease (ESRD); kidney biopsy.

Minimal change nephropathy is a common cause of nephrotic syndrome in adults.[1,2] In children, minimal change nephropathy frequently follows a benign course, and most cases go into remission before or at puberty.[3] Nonetheless, a higher rate of disease relapse during adulthood despite the availability of potent immunosuppressive agents has been shown in recent studies.[4,5] Our recent study showed that many patients with childhood-onset minimal change nephropathy still experienced relapse after they became adults, and extended use of corticosteroid and immunosuppressive agents leads to a considerable risk of treatment-related complications.[6]

Although there are many published studies of pediatric patients with minimal change nephropathy, few studies focus on adult patients,[7-13] and the results often are conflicting. A recent review of 50 Chinese patients with adult-onset minimal change nephropathy showed that the clinical presentation of older patients with minimal change nephrotic syndrome was similar to that of younger ones aside from a higher prevalence of hypertension.[12] In this study, steroid responsiveness was similar between older and young patients, although older ones tended to have fewer relapses and need fewer second agents for relapse treatment.[12] In contrast, another study of 95 adult patients with minimal change nephropathy found that more than one-quarter of patients were steroid resistant, another quarter were frequently

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relapsing, and a substantial proportion of frequently relapsing patients developed steroid dependence.[13] The aim of this study is to evaluate the long-term outcome of patients with biopsy-proven adult-onset minimal change nephropathy.

METHODS

Patient Characteristics

We identified 349 adult patients (aged ≥ 18 years) in our hospital with a pathologic diagnosis of minimal change nephropathy from 1984 until 2004. All patients had reached adulthood at the time of diagnosis, and based on the review of available clinical records, none of the patients had a history of nephrotic syndrome as a child or teenager. Patients with obvious secondary causes (eg, concomitant Hodgkin disease) were excluded. Nine patients were excluded because of the loss of clinical records (6 cases) and duplicated biopsy registration (3 cases). Clinical records of the remaining 340 patients were reviewed; relevant data for the course of disease, treatment regimen and response, disease outcome, medical problems after diagnosis, and cause of death were collected.

Treatment Protocol

The treatment regimen in our hospital for the initial episode of biopsy-proven minimal change nephropathy in adults generally was daily prednisolone (0.5-1 mg/kg/d, up to 60 mg/d), which was maintained for at least 4 weeks if there was complete remission or for a maximum of 16 weeks if complete remission was not achieved. After remission, corticosteroid dosage generally was tapered over 6 months. For relapse episodes, the same initial corticosteroid dosage generally was used, followed by gradual tapering of the dosage after remission was achieved. For patients with a contraindication to or intolerance of high-dose corticosteroids, patients with frequent relapses, or those dependent on corticosteroids, second-line agents such as cyclophosphamide, cyclosporine, or levamisole were used. The choice of second-line agent was decided by the individual nephrologists, although cyclophosphamide (2 mg/d orally for 8-12 weeks) generally was preferred, except for hepatitis B virus (HBV) carriers, for whom cyclosporine (3-5 mg/kg/d in 2 divided doses) was preferred. During the study period, we did not have a policy of universal prophylactic antiviral agents for long-term HBV carriers undergoing immunosuppressive therapy. Angiotensin-converting enzyme inhibitors often were used if there was residual proteinuria despite corticosteroid therapy. The decision of performing a second kidney biopsy was made by individual nephrologists. In general, patients with treatment-resistant disease were considered for a second kidney biopsy.

Definitions

The definitions of clinical response have been described.[13] Remission is defined as daily urine protein excretion < 0.3 g/d, urine protein-creatinine ratio < 0.3 mg/mg, or trace or negative results on repeat urine albumin dipstick. Time to remission is time from initiation of therapy to the first day on which remission is observed. Steroid resistance is defined as not achieving remission despite at least 16 weeks of prednisone (≥20 mg/d) treatment. Relapse is defined as increased protein excretion to >3 g/d or protein-creatinine ratio > 3 mg/mg. Frequent relapse is defined as 4 or more relapses within 1 year. Steroid dependence is defined as relapse upon tapering corticosteroid therapy or within 4 weeks of discontinuing corticosteroid therapy and the need for long-term maintenance corticosteroid therapy. Persistent proteinuria is defined as protein excretion of 0.5 to <3 g/d or protein-creatinine ratio of 0.5 to <3 mg/mg on 3 consecutive tests, without hypoalbuminemia or clinical edema. Permanent remission is defined as remaining relapse free at the last follow-up, with a relapse-free period of a minimum of 2 years without immunosuppressive medication.

Medical Problems After Diagnosis

Because it is difficult to determine whether a medical problem represents a delayed complication of the disease or its treatment, we defined a list of medical problems a priori and all cases are counted irrespective of the time lapse after the initial presentation. Parameters reviewed include persistent proteinuria, diabetes, hypertension, cardiovascular disease, cerebrovascular disease, avascular bone necrosis, any fracture, peptic ulcer disease, venous thromboembolism, any cancer, tuberculosis, other major infections, flare of chronic HBV infection, liver cirrhosis, and neuropsychiatric problems. Hypertension is defined as blood pressure > 140/90 mm Hg or need of antihypertensive treatment.[14] The prevalence of obesity is not reviewed because missing data for body weight are common. Major infection is defined as any infection that required hospital admission or parenteral antibiotic treatment.

We also review kidney function at the last available clinic visit. Kidney function is represented by glomerular filtration rate (GFR) as estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation.[15] Renal survival and patient survival also were analyzed. For renal survival, initiation of renal replacement therapy or death from uremia is counted as an event; death from other causes is censored. For patient survival, all deaths before and after the initiation of renal replacement therapy are counted as events.

Statistical Analysis

Statistical analysis was performed by SPSS for Windows software, version 18.0 (SPSS Inc). Data are expressed as mean ± standard deviation or median and interquartile range (IQR) as appropriate. To determine the relation between treatment response and clinical outcome, patients are classified into 4 groups for analysis: no relapse, infrequent relapse (patients who had at least one relapse episode but did not fulfill criteria for frequent relapse), frequent relapse, and primary steroid resistance (see previous section for definitions).

Data between groups were compared by χ^2 test, one-way analysis of variance, or Mann-Whitney U test, as appropriate. The relation between time to remission and age of presentation was explored by Spearman rank correlation. Patient and renal survival rates were calculated from the time of kidney biopsy and were compared between groups, as well as between patients 50 years or older and those younger than 50 years by Kaplan-Meier estimate and log-rank test. Because the 4 treatment response groups differed with regard to several demographic and clinical characteristics at baseline, a Cox proportional hazard model was constructed for patient survival to adjust for potential confounders. In addition to treatment response groups, we added age at presentation, sex, baseline estimated GFR (eGFR), preexisting hypertension, and history of acute kidney injury for construction of the Cox model. Because there is substantial variation in age of presentation and previous studies suggest that minimal change nephropathy in young adults and those older than 50 years may have a different treatment response[12,13] and pathogenesis,[16] we also compare patient and renal survival between patients 50 years or older and those younger than 50 years in each treatment response group. $P < 0.05$ is considered statistically significant. All probabilities are 2 tailed.