Original Article

Idiopathic minimal change nephrotic syndrome in older adults: steroid responsiveness and pattern of relapses

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Abstract

Introduction. Minimal change nephrotic syndrome (MCNS) is a common form of nephrotic syndrome in children and young adults. We investigated its clinical presentations, steroid responsiveness, subsequent clinical course and patterns of relapse in older adults in whom it was diagnosed after the age of 50 years.

Methods. The clinical records of renal patients followed-up in a single out patient clinic were retrieved and those patients with biopsy-proven MCNS were included. Patients in the 18–50-year age range (Group A) at the time of biopsy were compared with those older than 50 years (Group B) with regard to baseline demographic data, clinical features and outcome of treatment.

Results. In all, 50 patients were studied, 35 in Group A (age at diagnosis: 38.8 ± 11.91 years) and 15 in Group B (age at diagnosis: 70 ± 6.85 years), with an overall follow-up duration of 72.08 ± 63.42 months. Group B had a higher prevalence of hypertension and lower creatinine clearance at presentation, but the values of creatinine clearance for both groups were comparable with age-matched controls. One patient from Group B and two from Group A had spontaneous remission. Complete remission was achieved in 9.09, 45.45, 90.91 and 100% of Group B patients after 2, 4, 8 and 16 weeks of steroid therapy, respectively. The median time to complete remission and the duration of steroid treatment were similar for both groups. From Group B five patients and 22 patients from Group A relapsed during follow-up (P = 0.055), with similar proportions of each group being early relapers or frequent relapers. The average number of relapses was 2.06 episodes for Group A, compared with 0.87 episodes for group B (P = 0.062). Second agents were used in 20 Group A and four Group B patients (P = 0.048). Complications of treatment were more common in Group A. None of the patients developed doubling of serum creatinine during follow-up.

Conclusions. Clinical presentations of older patients with MCNS were similar to younger patients apart from the age-related decline of renal function and higher prevalence of hypertension. Both groups have similar steroid responsiveness, but older patients tend to have fewer relapses and require fewer second agents for treatment of relapses.

Keywords: adult; clinical outcome; MCNS; minimal change nephrotic syndrome; relapse; responsiveness; steroid

Introduction

Minimal change nephrotic syndrome (MCNS) is the predominant form of nephrotic syndrome in children [1]. Although relapses are common, childhood-onset MCNS usually runs a benign clinical course with preserved renal function in long-term follow-up [2]. On the other hand, adult-onset MCNS has been associated with a higher prevalence of hypertension, renal impairment and a slower response to steroids, but a lower tendency to relapse [3,4]; however, relatively little is known about MCNS in older adults. We therefore performed a retrospective review to characterize the clinical presentations, steroid responsiveness, subsequent clinical course and patterns of relapse of MCNS in older adults and made, whenever appropriate, comparisons with younger patients. The use of second therapeutic agents and potential treatment-associated complications were also studied.
Subjects and methods

The clinical records of patients followed-up in the renal clinic in Queen Mary Hospital were retrieved, and those patients with a histological diagnosis of MCNS were reviewed. Only patients of Chinese origin were included. Any patient who had underlying secondary causes for MCNS, concomitant pathology on renal biopsy, <18 years of age at the time of histological diagnosis of MCNS, or had been followed for <6 months was excluded. Baseline demographic data, serum albumin, serum creatinine, daily urine protein excretion, serum cholesterol, serum triglyceride and 24-h creatinine clearance were obtained. Concomitant medical conditions, in particular hypertension and diabetes mellitus, were documented. Patients were divided into two groups according to their age at the time of diagnosis—younger adults (Group A), who were between 18 and 50 years of age, and older adults (Group B), who were older than 50 years. The clinical manifestations, duration of steroid treatment, occurrence and time to complete remission, presence and number of relapses, time to first relapse, use of second agents and steroid dependence of patients were investigated and compared between the two groups. Clinical outcomes including doubling of serum creatinine and complications of treatment were analysed. In order to adjust for the effect of age on renal function, 10 healthy age-matched controls were included for comparing creatinine clearance in both groups, with five controls for each group.

Renal biopsy

All of the histology slides were reviewed by a single pathologist. The histological criteria for diagnosing MCNS included: diffuse effacement of foot processes of podocytes on electron microscopy, absence of electron dense deposits or thickening of basement membrane, negative immunofluorescence and absence of segmental sclerosis. Patients with concomitant glomerular or interstitial pathology on initial renal biopsy were excluded. Also excluded were patients with an initial histological diagnosis of MCNS who had a steroid-resistant course and a subsequent renal biopsy showing concomitant glomerular pathology.

Treatment protocol

All patients were treated with oral prednisolone (0.8 mg/kg/day) for biopsy-proven MCNS with a weekly dose tapered depending on clinical response. Steroid withdrawal was considered if patients had been in complete remission for at least 3 months. Second agents for treating relapses were considered on an individual basis if an increase in the steroid dose alone failed to induce complete remission.

Definitions

‘Complete remission’ was defined when clinically supported by a daily urine protein excretion <0.3 g and trace or negative evidence of albumin on urine dipstick tests. ‘Relapse’ was defined clinically when the attending physician judged it necessary to step up immunosuppressive therapy—supported by daily urine protein excretion of >3.0 g with 3+ or 4+ results on urine albumin dipstick tests. ‘Frequent relapse’ was defined as either two or more relapses within 6 months or four or more relapses within 1 year. ‘Early relapse’ was defined as relapse within 6 months after initial complete remission. ‘Steroid dependence’ was defined as relapse on tapering steroid therapy or within 4 weeks of stopping steroid therapy and the need for long-term maintenance steroid treatment.

Statistical analysis

Student’s t-test, χ² test, Fisher’s exact test and Mann–Whitney test were used where appropriate for between-group data analysis, with the SPSS 10.0 software. Continuous variables were expressed as mean ± SD or median values. P-value at or <0.05 was considered statistically significant.

Results

There were 74 patients with MCNS followed-up in the renal clinic of whom 50 fulfilled the inclusion criteria of this review. The reasons for exclusion of the other 24 patients were: <18 years of age at the time of diagnosis (n = 11), follow-up duration <6 months (n = 5), non-Chinese patients (n = 3), subsequent diagnosis of focal segmental glomerulosclerosis (n = 3), concomitant pathology on renal biopsy (n = 1) and defaulted follow-up (n = 1). The mean age for the entire cohort was 48.3 ± 18.08 years with a mean follow-up duration of 72.08 ± 63.42 months. Group A included 35 patients with a mean age of 38.8 ± 11.91 years at the time of diagnosis and Group B had 15 patients with a mean age of 70 ± 6.85 years. The two groups had similar baseline characteristics at presentation, but patients from Group B had a higher prevalence of hypertension (P = 0.050), higher serum creatinine (P = 0.007) and lower creatinine clearance at presentation (P = 0.003) (Table 1). However, the values for creatinine clearances of either group and their respective age-matched controls were found to be similar (Table 2). Acute renal failure complicating nephrotic syndrome requiring temporary haemodialysis occurred in one patient from Group A, who subsequently had full recovery of renal function.

Two patients from Group A and one from Group B had spontaneous remission before treatment was started. The other patients were started on oral steroids. The median duration of steroid treatment was 13 months for Group A compared with 7 months for Group B (P = 0.138). Complete remission was achieved in 9.09, 45.45, 90.91 and 100% of Group B patients and 15.63, 62.5, 87.5 and 93.75% of Group A patients after 2, 4, 8 and 16 weeks of steroid therapy, respectively. All but one patient from Group A achieved complete remission with steroid therapy alone—and that patient eventually achieved complete remission after the addition of cyclophosphamide (CTX) and, subsequently, cyclosporin A. The two groups had similar complete remission rates at the respective time points and similar median times to complete remission (Group A = 4 weeks, Group B = 5 weeks).
complete remission, and one was given mycophenolate mofetil. In Group A, a patient was given azathioprine and had three patients receive- ed levamisole, which induced complete remission in all. In Group A, six patients were given cyclosporin A and one Group B patient was given mycophenolate mofetil. CTX was administered in 19 patients (Group A) and in two cases for the initial episode along with other secondary agents.

Among relapsing patients, similar proportions of both groups were early relapsers or frequent relapsers, as compared with 0.048). In Group A, 12 patients and three patients in Group B were considered steroid-dependent (P = 0.312). A schematic representation of the clinical course of patients with MCNS is given in Figure 1.

Second agents were used in 24 patients (Group A = 20 patients, Group B = four patients, P = 0.048). In 22 cases they were given for the treatment of relapses and in two cases for the initial episode along with steroids. CTX was administered in 19 patients (Group A = 16 patients, Group B = three patients), and induced complete remission in 18 (94.74%) patients. Cyclosporin A was given in six Group A and one Group B patients and produced complete remission in all. In Group A, three patients received levamisole, which induced complete remission in two patients. Finally, one patient in Group A was given azathioprine and had complete remission, and one was given mycophenolate mofetil without response.

Overall, treatment-related side effects were uncommon for Group B patients—most were steroid related, and included urinary tract infection (n = 1), proximal myopathy (n = 1) and steroid-induced osteoporosis (n = 1) complicated by femoral neck fracture requiring operation. There were no treatment-associated complications related to the use of second agents in Group B patients. As for Group A patients, most complications were related either to the use of steroids or CTX. Those included: gastrointestinal upset (n = 1), gastrointestinal bleeding (n = 1), perforated peptic ulcer (n = 1), cutaneous fungal infection (n = 1), glaucoma and cataract (n = 1), avascular necrosis of femoral head (n = 1), hair loss (n = 2) and neutropenia (n = 1). No significant side effects were reported for the use of cyclosporin A or levamisole.

Serum creatinine and creatinine clearances were significantly different in the two groups at the end of follow-up (Group A vs Group B; serum creatinine: 85.65 ± 17.51 vs 105.13 ± 33.36 μmol/l, P = 0.010; creatinine clearance: 94.64 ± 36.8 vs 50.23 ± 19.57 ml/min, P = 0.002) while other biochemical parameters were similar. No mortality or significant morbidity was noted in either group. In particular, none of the patients from either group developed progressive renal failure, and doubling of serum creatinine levels was not observed in follow-up.

**Discussion**

MCNS accounted for 8.8% of renal biopsies among Chinese patients who presented with nephrotic syndrome in our locality [5]. Apart from MCNS, other...
recognized causes of nephrotic syndrome in older patients include membranous glomerulonephritis (MGN), primary amyloidosis and focal segmental glomerulosclerosis (FSGS) [6,7]. Despite the similar clinical presentations of these other causes, their responses to treatment and their impact on renal survival are markedly different. In one series, MGN was found to be the most common cause of nephrotic syndrome in elderly patients, but its prognosis was poor—with most patients eventually dying or going into end-stage renal failure [8]. Renal biopsy is therefore important for making the correct diagnosis, predicting outcome and guiding subsequent therapy considering the potential treatment-associated complications of corticosteroids and second-line immunosuppressive agents. Moreover, certain cases of FSGS may be misdiagnosed as MCNS on initial renal biopsy due to the focal nature of the lesions, and repeating renal biopsy may sometimes be necessary in cases of relapsing and steroid-resistant MCNS.

The initial clinical presentations of older and younger patients from our cohort were found to be similar, apart from a higher prevalence of hypertension and lower creatinine clearance in older patients. Such differences are most likely due to the age-related decline in renal function and increased prevalence of hypertension rather than to the presence of MCNS, as supported by the fact that creatinine clearances in the two groups and their age-matched controls were similar. The overall rate of steroid responsiveness in our cohort approached 90% by the eighth week of treatment for both younger and older patients, which is similar to the rate in childhood-onset disease, and is relatively higher compared with other series of adult-onset MCNS, which are based mainly on Caucasian patients [3,4,9]. On the other hand, a similarly favourable response to steroid therapy has also been noted in adult-onset MCNS in two Asian series [10,11]. It seems that ethnic differences could exist in adult-onset MCNS, and Asian patients could be more steroid responsive. Concerning relapses, it has been shown that, in childhood-onset disease, frequency of relapses was strongly related to age at onset, with the younger patients having a tendency to have a more frequently relapsing course [3]. Similar tendencies have been noted in adult patients with MCNS by other investigators. Huang et al. showed that patients >40 years of age tend to have a relapsing course of MCNS during follow-up [10]. In a Japanese series, it was found that a negative correlation existed between the age at onset of MCNS and the number of relapses per patient per year, and that the mean number of relapses per patient per year was significantly higher for patients who were <40 years at their initial presentations of MCNS [12]. Our data are in keeping with the observations that older patients tend to have more benign courses. It is likely that MCNS in different age groups merely represents different parts of a spectrum of the same

Fig. 1. Clinical course of patients with MCNS.
underlying disease, with the older patients running a less relapsing course with sustained, long-term remission on follow-up.

There is little data with regard to complete remission rates for the use of cytotoxic agents in adult-onset MCNS, but the complete remission rate of 94.74% with CTX for both groups in our series seems to be higher than in others [3,4]. However, the small number of our patients requiring second agents precludes meaningful comparisons of the exact response rate, and studies involving more patients are needed. Finally, one important concern about steroid and immunosuppressive therapy in patients with advancing age is the potential of treatment-related complications, but a higher incidence of treatment-related complications was not observed in our series. In fact they were less common in older than younger patients—and this was considered most likely due to the relatively short total duration of steroid treatment for older patients with MCNS and fewer relapses with infrequent call for second agents during follow-up.

In conclusion, older adults with MCNS have similar clinical presentations and share similar rates of steroid responsiveness with their younger counterparts, but tend to have fewer relapses and require fewer second agents for the treatment of relapses. Steroid treatment is effective in older patients with MCNS, has few treatment-related complications, and should therefore be given in the usual manner.

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References


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