Review article

Idiopathic nephrotic syndrome in the elderly

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Abstract

The most frequent primary glomerular diseases (PGD) associated with nephrotic syndrome (NS) in the elderly are membranous nephropathy (MN), minimal change nephropathy (MCN), and focal and segmental glomerulosclerosis (FSGS).

In older patients MN may be secondary to drugs or neoplasia in 20 to 25% of cases. The natural renal outcome of idiopathic MN is similar in elderly patients and in those of the second age. However, elderly patients are more exposed to the extra-renal complications of NS. Corticosteroids alone do not seem to modify the course of the disease. A 6-month regimen with corticosteroids alternated to chlorambucil, which has proven to improve the outcome of MN in adults, may increase the chances of remission and protect renal function also in the elderly patients but side effects increase with age.

Elderly patients with MCN are more prone than younger adults to the complications of the NS and to the development of renal failure. Only 60% of older patients enter remission with an 8-week course of prednisone, but about 80% can achieve complete remission with corticosteroids if treatment is prolonged to 12-16 weeks. Relapses are more rare in the elderly. In patients with contraindications to prolonged corticosteroid therapy, a course of 12 weeks with a cytotoxic agent may obtain stable remission in most cases.

Little information is available about the natural course and the management of idiopathic FSGS in the elderly. A recent report showed that more than 40% of older patients may obtain stable remission after an initial treatment with corticosteroids for 6 months. For those patients who do not respond or have contraindications to steroid therapy, a cautious trial with cyclophosphamide may be tried.

Introduction

Little attention has been paid so far to the problems of primary glomerular disease (PGD) in the elderly. The prevailing opinion is that these diseases become increasingly rare with advancing age [1]. However, this impression is not based on epidemiological data but rather reflects the reluctance of many nephrologists to perform a renal biopsy in older patients. As a matter of fact, several studies based on histological diagnosis reported a similar prevalence of PGD in the elderly and adults [2–13]. The best epidemiological study about the incidence of glomerulonephritis (GN) in the elderly was performed by Simon et al. [13] in the French region of St. Brieuc. These investigators conducted a prospective study on the incidence of PGD diagnosed by renal biopsy for a period of more than 15 years. The cumulative annual incidence of PGD was similar in patients older than 60 years and in younger adults (8.5 vs 8.4/10^5 inhabitants/year, respectively). However, the distribution of the causes of PGD as assessed by renal biopsy was different. Thus the annual incidence of IgA nephritis was lower in elderly patients than in younger adults, while pauci-immune crescentic GN was more frequent in the elderly. Among the PGD asso-

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associated with the NS the most frequent in the elderly was MN with an annual incidence of 2.5 cases/10^5 inhabitants/year, which was 2.8 times higher than in younger adults. In contrast, the annual cumulative incidence of MCN and of FSGS was 0.7 cases/10^5 inhabitants/year, similar to that observed in younger adults.

In this paper we will review the main clinical characteristics, the natural course and the response to treatment of MN, MCN and FSGS which are the primary glomerular diseases more frequently associated with the nephrotic syndrome in the elderly.

Membranous nephropathy

Several reports have pointed out that MN is the most common GN in the elderly [2–4, 9, 11, 13]. In 20–25% of older patients with MN an identifiable associated or underlying condition can be found [15]. The two most common causes of secondary MN are drugs (especially nonsteroidal anti-inflammatory drugs) and cancer [16]. Some studies reported that 16 to 20% of older patients with MN had an underlying malignancy [3, 8, 14, 16]. In view of the strong association of cancer and MN in the elderly, an extensive research of underlying neoplasia should be included in the work-up of older patients with MN. In this regard, one should recall that the most frequent localizations of cancer in MN are lung, colon, rectum, kidney, breast, and stomach in that order [17].

At presentation, at least 85% of elderly patients with idiopathic MN have NS [2–4, 9, 11, 18]. About 40% are hypertensive [9], 30 to 90% have hematuria [2, 9], and some 15% have renal failure [9]. There is little information about the natural course of MN in the elderly patients. Some investigators reported that age unfavorably influenced the outcome [19–21] but others found that age is not a prognostic factor [22–24]. However, very few patients older than 60–65 years were studied in those reports. We followed the course of 12 patients with idiopathic MN older than 65 years never treated with corticosteroids or immunosuppressive agents [18]. After a mean follow-up of 7.5 years, three had died respectively from cardiac infarct, cancer and pneumonia, one developed end stage renal disease, and three others had doubling of serum creatinine. Only one patient entered a complete spontaneous remission of proteinuria. Thus, some 58% of the elderly patients either died or showed renal function deterioration. This outcome was slightly worse than that we observed in younger adults. Of 49 untreated nephrotic patients with a mean age of 47 years, followed for a mean period of 9 years, 7 (14%) had a complete remission at the last visit and 22 (45%) either died or developed renal failure. Of 12 deaths, 5 were caused by cardiac infarct, 2 by cancer, 2 by stroke and pulmonary embolism [23].

Only sporadic reports about the effects of therapy in the elderly patients with MN are available. In a retrospective analysis of the literature, Bolton [5] found that 22 of 51 (43%) patients treated with corticosteroids entered remission of the NS. However, these data are difficult to interpret, as there was not sufficient information either about the length of follow-up or about the doses, the length and the tolerance of corticosteroid therapy. It is not clear whether the results referred to the remission as a first event or at the last observation. In a retrospective study, we reviewed the outcome of 41 nephrotic patients with idiopathic MN older than 65 years [18]. All patients had a potential follow-up of at least 1 year. Twelve patients never received corticosteroid or immunosuppressive agents, 14 were treated with corticosteroids alone for 3–12 months, and 15 were treated with a six-month course of methylprednisolone (MP) alternated with chlorambucil [25]. At the last visit, there were significantly more remissions of the NS, either complete or partial, in the group receiving MP plus chlorambucil (73%) than in untreated patients (25%) or given corticosteroids alone (21%). Some 50% of untreated patients and 36% of patients given corticosteroids developed renal dysfunction while only 13% of patients treated with MP and chlorambucil, demonstrated an increase in serum creatinine (Table 1). However, the mean follow-ups of these groups were different. In order to reduce this bias, we evaluated, the mean plasma creatinine and mean urine protein excretion only in 13 patients followed for at least 5 years [18]. After 5 years, the mean plasma creatinine doubled in 7 untreated patients (from 113±14 to 239±287 nmol/l) while it remained stable in 6 patients given MP and chlorambucil (from 112±29 to 124±30 nmol/l). Proteinuria decreased from 6.8±1.6 to 1.1±1.4 g per day in this latter group while it did not modify (4.7±3.1 vs 4.8±5.7 g per day) in untreated patients. Only two patients given corticosteroids alone were followed for 5 years, so that analysis was not made for them. Although retrospective, these data would indicate that treatment with MP and chlorambucil can improve the chances of remission and can protect renal function in the elderly. However, the incidence and the severity of side-effects with this regimen in older patients were high. Of 15 treated patients, 1 developed sideroblastic anemia, 3 infections, 1 severe