ORIGINAL ARTICLE

Port J Nephrol Hypert 2009; 23(1): 49-52
Advance Access publication 19 November 2008

Membranous nephropathy: a single centre experience

Flora Rico Sofia, Helena Sá, Jorge Pratas, Henrique Gomes, Mário Campos

Department of Nephrology, Hospitais da Universidade de Coimbra. Coimbra, Portugal.

Received for publication: 25/04/2008
Accepted in revised form: 09/10/2008

ABSTRACT

Membranous nephropathy is among the most common causes of the nephrotic syndrome in adults. While some patients with membranous nephropathy achieve a spontaneous remission, renal function continues to deteriorate in others.

A treatment strategy is needed to appropriately administer conservative treatment to the low-risk group and immunosuppressive therapy to those at higher risk of renal deterioration.

We retrospectively studied 70 nephrotic syndrome patients with biopsy-proven idiopathic membranous nephropathy, registered in our department from 1987 to 2006.

Symptomatic management for proteinuria and hypertension was the base of treatment. The immunosuppressive therapy regimens were oral prednisone for six months (Group I) or ciclosporin given for twelve months, accompanied by prednisone until a response was achieved (Group II).

After a follow-up of five years, the 13 patients treated just with prednisone had a better outcome than the 12 patients treated with ciclosporin and prednisone. We conclude that Group II patients had an adverse profile of prognostic factors which influenced the evolution of membranous nephropathy. This is the experience of our centre and does not necessarily demonstrate the best choice of therapy.

The steroids-ciclosporin combination is the one most currently studied and preferred, while newer forms of immunosuppressive therapy are under study. Improved understanding of the role of complement in the pathogenesis of membranous nephropathy and of the cellular response creates several new opportunities for therapeutic intervention that may benefit patients with membranous nephropathy in the future.

Key-Words:
Ciclosporin; membranous nephropathy; nephrotic syndrome; prednisone; prognostic factors.

INTRODUCTION

Membranous nephropathy (MN) is a common type of glomerular disease, accounting for 30-40% of cases of nephrotic syndrome in adults. About 75% of cases are idiopathic and 25% are secondary to a wide variety of causes, including neoplasia, infections, autoimmunity and drugs.

The typical presenting feature of idiopathic MN is nephrotic syndrome (80%) or persisting non-nephrotic proteinuria (20%). Presenting features are not distinctive enough to permit a diagnosis without a renal biopsy examination. The morphology features are characteristic and include gradual thickening of the capillary wall caused by the *in situ* deposit of immune complexes accompanied by new basement membrane synthesis.

The natural history of the untreated disorder is variable. Spontaneous remission (complete or partial) of proteinuria, usually accompanied by stable

renal function, occurs in 40% of patients and an identical percentage slowly progress to end-stage renal disease (ESRD). Factors associated with a progressive course include older age at onset, male gender, persisting nephrotic range glomerular proteinuria, reduced renal function at onset and advanced glomerular damage with chronic tubulointerstitial fibrosis.

PATIENTS AND METHODS

We analysed 95 consecutive patients with newly diagnosed, biopsy-proven membranous nephropathy (MN), who presented at the Nephrology Department with proteinuria or oedema from 1987 to 2006. Eighty-three patients had nephrotic syndrome and twelve non-nephrotic proteinuria. We retrospectively studied 70 nephrotic syndrome patients with idiopathic membranous nephropathy.

Excluded from the study were those patients with systemic lupus erythematosus or any other systemic disease, diabetes mellitus, chronic infectious diseases (including hepatitis B and C viruses and HIV infection), drug-induced MN, haematological diseases and every patient in whom a diagnosis of secondary MN was established during the study.

The morphology criteria used for diagnosis were those of Ehrenreich and Churg: stage I, subepithelial dense deposits; stage II, basement-membrane spikes (silver-staining segments of basement membrane between dense deposits); stage III, incorporation of the dense deposits in the basement membrane; and stage IV, markedly thickened basement membrane.

Salt restriction, diuretic therapy, lipid lowering agents and antihypertensive drugs (including ACE inhibitors as antiproteinuric agents) were the basis of treatment.

Immunosuppressive treatment consisted of either oral prednisone for six months (Group I) starting with 1 mg/kg/day and 0.5 mg/kg every other day from third to sixth month or ciclosporin for twelve months at a dose of 5 mg/kg/day given in two doses, to maintain whole blood trough levels of 100-150 ng/ml, accompanied by simultaneous prednisone given every other day at a dose of 1-2 mg/kg (Group II). Prednisone was quickly tapered once a response was achieved.

Complete remission was defined as a proteinuria ≤0.3 g/24h with normal serum albumin. Partial remission was defined as a proteinuria between 0.3 and 3.5 g/24h. Nephrotic syndrome was defined as a proteinuria ≥3.5 g/24h accompanied by hipoalbuminaemia (≤3.5 g/dl). Renal insufficiency was defined as a serum creatinine (S_{Cr}) ≥1.5 mg/dl together with a creatinine clearance (C_{Cr}) ≤60 ml/m, in at least three consecutive determinations.

The X^2 test and Student *t* test were used for statistical analysis where appropriate. *P* values ‹0.05 were considered statistically significant.

RESULTS

We retrospectively studied 70 nephrotic syndrome patients with idiopathic membranous nephropathy (43 men and 27 women; mean ±SD age, 50±17 years). Using Ehrenreich and Churg staging, 30% of patients were stage I, 18.6% stage II and 51.4% stage III.

Baseline clinical and laboratory data (mean±SD) for these 70 patients at date of diagnosis were hypertension in 54.3%, and chronic renal failure in 15.7%, serum creatinine 1.08±0.49 mg/dl, urinary protein excretion 9.8±4.5 g per 24 hours, serum albumin 2.16±0.77 g/dl and serum cholesterol 358.4±116.2 mg/dl.

Treatment consisted of ciclosporin and prednisone (45.3% of patients, Group II), prednisone (25%, Group I), cyclophosphamide (14.1%) and symptomatic management of proteinuria and hypertension with no immunosuppressive treatment (15.6%).

As previously stated this is a retrospective study.

Treatment was chosen according to the gravity of clinical and laboratory presentation.

Baseline clinical and laboratory data (mean±SD) of Group I were age 47.8±16.9 years, 50% of patients with arterial hypertension and 6.3% of patients with serum creatinine above 1.5mg/dl. Group II data

Table I

Baseline clinical and laboratory data (mean±SD)

	Age	HTA	S_{Cr}>1.5 mg/dl	Proteinuria (g /24h)	S_{alb} (g/dl)	Stage: I/II/III %
Group I	47.8±16.9	50%	6.3%	7.9±4.4	2.6±0.9	53.8/23.1/23.1
Group II	41.6±13.3	51.7%	13.8%	11.5±9.5	1.8±0.7	27.2/36.4/36.4

S_{Cr} – serum creatinine; S_{alb} – serum albumin

Table II

Evolution after a follow-up of 5 years

	Group I	Group II
Complete remission	76.9 %	25 %
Partial remission	23.1 %	41.7 %
Nephrotic syndrome	0	25 %
ESRD – HD	0	8.3 %

ESRD – HD: End-stage renal disease requiring regular dialysis

(mean±SD) were age 41.6±13.3 years, 51.7% of patients with arterial hypertension and 13.8 % of patients with serum creatinine above 1.5mg/dl.

Group II patients had more advanced glomerular changes (Ehrenreich and Churg staging) than Group I patients; stage I, 27.2%, stage II, 36.4% and stage III, 36.4% *vs*. stage I, 53.8%, stage II, 23.1% and stage III, 23.1%, in turn.

Group II patients had greater urinary protein excretion and lower levels of serum albumin than Group I patients; 11.5±9.5 g per 24 hours, 1.8±0.7 g/dl and 7.9±4.4 g per 24 hours, 2.6±0.9 g/dl respectively.

Significance for the difference of values data between Group I and II are: Student *t* test: p=0.014 (serum albumin) and p=0.119 (proteinuria). Group II patients had a higher prevalence of renal failure (Student *t* test: p=0.011).

Group I initially had 16 patients, dropping to 13 within 5 years as a result of patient drop-out from follow-up. Group II began with 29 patients, ending with 12. We analysed the evolution of the two groups (total of 25 patients) after a follow-up of five years.

Group I patients (13 patients) had complete remission (76.9%) and partial remission (23.1%). Group II patients (12 patients) had complete remission (25%), partial remission (41.7%), nephrotic syndrome (25%) and end-stage renal disease requiring regular dialysis (8.3%). Chi-square test: p=0.0094.

Eight of the MN patients (total 95 patients) developed end-stage renal disease requiring regular dialysis, after a mean interval of 54.4±41.3 months.

DISCUSSION

After five years, in terms of complete remission or no remission, Group I patients had a better outcome than Group II patients, as calculated with X^2 test: p=0.0094. The selection of patients for treatment based on an adverse profile of prognostic factors may also result in a selection of patients for treatment who are intrinsically less likely to respond to treatment. This study is the experience of our centre and does not necessarily demonstrate the best choice of therapy.

Treatment of idiopathic MN is a controversial issue. Studies into the natural history of non-treated idiopathic MN patients have reported a considerable number of spontaneous remissions (ranging between 20 to 40%) and the prevalence of end-stage renal disease is approximately 14% at 5 years and 40% at 15 years[1-7].

The administration of immunosuppressive therapies to all patients with idiopathic MN has been criticised, as many patients who would evolve into spontaneous remission are exposed to the risks of immunosuppressive therapies[2,4-5].

Immunosuppressive therapies should therefore be restricted to those patients at highest risk of progressive disease. Several clinical and biochemical

parameters have been proposed to establish this selection: men over the age of 50 years, sustained massive proteinuria values, elevation of serum creatinine at presentation and advanced glomerular damage with chronic tubulointerstitial fibrosis[1-8].

Currently the trend is to use ciclosporin given for 6 to 12 months at a dose of 4 to 6 mg/kg per day (divided into two doses) to maintain whole blood trough levels of 100-150 ng/ml, accompanied by simultaneous prednisone given every other day (1 to 2 mg/kg every other day). Prednisone should be quickly tapered once a response is achieved[9-12].

Alternative agents in the treatment of MN have been tried. These include rituximab, adrenocorticotropic hormone, mycophenolate mofetil, intravenous immunoglobulin, pentoxifylline and tacrolimus. Long term outcome data are not available[13-18].

Recent molecular advances have identified podocyte-specific proteins that have been implicated in human disease. Genetic testing will not only allow early and accurate diagnosis of podocyte disorders to be made but will also be used for accurate diagnosis of diseases formerly called 'idiopathic'. It will also help define the subgroup of patients who will benefit from immunosuppressive medications, those who will experience disease recurrence after transplantation and those who will progress to end-stage renal disease.

Future directions in MN research will not differ from those into other autoimmune diseases in requiring a much better understanding of how tolerance is broken to selected self-antigens and how that loss of tolerance can be restored to halt the immune process that is the underlying mediator of the disease[19,20].

Conflict of interest statement. None declared.

References

1. K N Lai. Membranous nephropathy: When and how to treat. Kidney Int 2007; 71:841-842
2. Torres A, Domínguez-Gil B, Carreno A. Conservative versus immunosuppressive treatment of patients with idiopathic membranous nephropathy. Kidney Int 2002;61:219-227
3. Glassock R. Diagnosis and natural course of membranous nephropathy. Semin Nephrol 2003;23:324-332
4. Buf- Vereijken P, Branten A, Wetzels J. Idiopathic membranous nephropathy: Outline and Rationale of a treatment strategy. Am J Kidney Dis 2005;46:1012-1029
5. Goumenos D S, Kalliakmani P, Tsakas S, Sotsiou F, Vlachojannis J G. The remission of nephritic syndrome with cyclosporine treatment does not attenuate the progression of idiopathic membranous nephropathy. Clin Nephrol 2004;61:17-24
6. Yoshimoto K, Yokoyama H, Wada T. Pathologic findings of initial biopsies reflect the outcomes of membranous nephropathy. Kidney Int 2004;65:148-153
7. Praga M, Barrio V, Juárez G, Luno J. Tacrolimus monotherapy in membranous nephropathy: A randomised controlled trial. Kidney Int 2007;71:924-930
8. D'Amico G. Influence of clinical and histological features on actuarial renal survival in adult patients with idiopathic IgA nephropathy, membranous nephropathy and membranoproliferative glomerulonephritis: Survey of the recent literature. Am J Kidney Dis 1992;20:315-323.
9. Muirhead N. Management of idiopathic membranous nephropathy: Evidence-based recommendations. Kidney Int 1999;55(Suppl 70):47-55
10. Cattran DC, Appel GB, Hebert LA, *et al.* Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomised trial. Kidney Int 2001;59:1484
11. Cattran D. Management of membranous nephropathy: when and what for treatment. J Am Soc Nephrol 2005;16:1188
12. Alexopoulos E, Papagianni A, Tsamelashvili M, Leontsini M, Memmos D. Induction and long-term treatment with cyclosporine in membranous nephropathy with the nephrotic syndrome. Nephrol Dial Transplant 2006;21:3127-3132
13. Ruggenenti P, Chiurchiu C, Abbate M *et al.* Rituximab for idiopathic membranous nephropathy: who can benefit? Clin J Am Soc Nephrol 2006;1:738
14. Ponticelli C, Passerini P, Salvadori M *et al.* A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. Am J Kidney Dis 2006;47:233-240
15. Choi MJ, Eustace JA, Gimenez LF *et al.* Mycophenolate mofetil treatment for primary glomerular diseases. Kidney Int 2002;61:1098
16. Palla R, Cirami C, Panichi V *et al.* Intravenous immunoglobulin therapy of membranous nephropathy: Efficacy and safety. Clin Nephrol 1991;35:98
17. Ducloux D, Bresson-Vautrin, Chalopin JM. Use of pentoxifyline in membranous nephropathy. Lancet 2001;357:1672.
18. Perna A, StatSciD, Schieppati A *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy: A systematic review. Am J Kidney Dis 2004;44:385-401
19. Jefferson A, Shankland S. Division of Nephrology, University of Washington, Seattle, Washington. Editorial. Glomerular Disease: The Podocyte is ready for prime time and may already be center stage.Nephrology Self Assessment Program- Vol 5. Nº6. November 2006
20. Nangaku M, Shankland S, Couser W. Cellular response to injury in membranous nephropathy. J Am Soc Nephrol 2005;16:1195-1204

Correspondence to:
Dr Flora Rico Sofia
Department of Nephrology
Hospitais da Universidade de Coimbra
Praceta Mota Pinto
3030 Coimbra, Portugal
e-mail: fmdrs@iol.pt