

## PROFILE OF MEMBRANOUS NEPHROPATHY IN MOROCCAN PATIENTS: EXPERIENCE OF NEPHROLOGY DEPARTMENT IN RABAT- MOROCCO

M.Jdidou, A. Ermilo Haroun\*, T. Bouattar, L. Benamar, R. Bayahiya, N. Ouzeddoun

Service de Néphrologie – Dialyse et Transplantation Rénale, Ibn Sina University Hospital – Rabat, Morocco.

\* Département de santé publique, biostatistique et épidémiologie clinique, Université Mohamed V Rabat, Morocco

### ABSTRACT

**Introduction:** Membranous nephropathy is the most common cause of primary nephrotic syndromes in adults. Our study aims to describe the epidemiological, clinical, pathological and therapeutic aspects of patients with this condition in Morocco. **Patients and Methods:** We conducted a retrospective study in the nephrology department at Ibn Sina University Hospital in Rabat- Morocco, from January 2006 to December 2016. We included all cases of diagnosed MN, with a kidney biopsy and followed for at least 04 years. **Results:** Over 10 years, we identified 71 cases of MN; the mean age in our patients was 43.5 years old “[20- 76]” with a female predominance and a sex ratio of 0.8. Proteinuria was the main revealing sign; it was nephrotic in 87% of cases. Kidney failure was noted in 38%. Phospholipase A2 receptor antibodies were carried out in 43 cases and were positive in 24 patients (55.8%). Histologically, 47 patients had stage II MN, associated with interstitial fibrosis exceeding 50% in 10 patients. MN was idiopathic in 58 cases and secondary in 13. The etiologies retained were infectious (5 cases), autoimmune (5 cases) and neoplastic in 3 cases. Concerning idiopathic MN, all 58 patients received treatment with renin-angiotensin –aldosterone system blockers for 6 months. Twenty three of them received immunosuppressive therapy and only one patient received anti-CD20 therapy. Eighteen patients had complete remission after a mean follow-up of 8.4 months and 25 had partial remission. Five patients were in chronic renal failure and chronic end-stage renal failure was reported in 10 cases. Twelve patients relapsed after a mean delay of 20 months; seven of them were treated according to the classic Ponticelli protocol. Kidney failure at admission and interstitial fibrosis exceeding 50% were factors of poor renal prognosis. **Conclusion:** According to our study, primary MN is the most frequent in Moroccan patients; kidney failure at admission and interstitial fibrosis >50% seems to be associated to poor renal prognosis.

**Keywords:** Membranous nephropathy; Morocco; primary; prognosis.

### Corresponding Author:

Mariam Jdidou MD.

**Affiliation :** Service de Néphrologie – Dialyse – Transplantation Rénale. CHU Ibn Sina – Rabat, Morocco

**E-mail:** [jdidou.mariam@gmail.com](mailto:jdidou.mariam@gmail.com)

**ORCID ID:** <https://orcid.org/0009-0006-8421-754X>

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### INTRODUCTION

Membranous nephropathy (MN) is the most common cause of primary nephrotic syndrome (NS) in adults [1]. It manifests mainly as proteinuria (PU), often nephrotic. It is most often idiopathic (80% of cases), although it may be secondary. The clinical course of MN is variable: 15 to 30% of cases progress to spontaneous remission, and one-third of cases progress to end-stage chronic renal failure. Identification of the Anti-phospholipase A2 receptor antibodies (PLA2R) is a valuable biomarker for the diagnosis and follow-up of patients.

### OBJECTIVES OF THE STUDY

To describe the epidemiological, clinical, anatomopathological, and therapeutic aspects of all patients with MN in the Moroccan context, and to evaluate the predictive risk factors for progression to end-stage chronic renal failure.

### PATIENTS & METHODS

We conducted a retrospective study, including all MN cases diagnosed by kidney biopsy in the department of nephrology at Ibn Sina University Hospital in Rabat- Morocco from January 2006 to

December 2016. Our patients were identified from the register of pathology. The histological diagnosis was based on the pathological examination of the renal parenchyma obtained by kidney biopsy.

Inclusion criteria were: adulthood with a confirmed histological diagnosis of MN. Files with incomplete data were excluded. We collected demographic (age and gender) and clinical data (comorbidities, medical history and clinical presentation) from medical records. The biological parameters considered for the study were: serum protein, albumin, serum creatinine with the creatinine clearance according to the MDRD formula, 24 hour proteinuria. We have adopted the following definitions:

- Complete remission was defined by proteinuria < 0.3 g/24h, albuminemia > 30 g/l and normal kidney function.
- Partial remission is defined by 0.3 < Proteinuria < 3 g/24h, albuminemia > 30 g/l, and stable kidney function.
- The absence of remission is defined by the aggravation or the persistence of Proteinuria (PU) and/or renal failure, see the evolution towards end-Stage chronic renal failure.

A statistical analysis of the different data was carried out using the *Jamovi software Windows version 20*. The qualitative variables were described in number and percentage, and the comparative study was made by the chi-square or Fischer exact test. The variable Gaussian distribution quantities were expressed as mean and standard deviation, and were compared using the Student test. Quantitative variables with a non-Gaussian distribution were expressed in median and interquartile range. The comparative study was performed by the Mann Whitney test. p value was considered significant when less than 0.05.

## RESULTS

Over 10 years, we identified 71 cases of MN in our department with 40 women (56.3%) and 31 men (43.7%) [sex ratio=0.8]. The average age was 43.5 years old “[20-76]”. Proteinuria (PU) was the main

presenting sign. It was nephrotic in 87% of cases. Renal failure was noted in 33.8% of cases with a mean creatinine level of 201.5 μmol/l (Table 1). The anti-phospholipase A2 receptor antibodies (PLA2R) performed in 43 cases were positive in 24 cases (55.8%). Histologically, 47 patients (59.2%) had Bariety stage II MN, associated with interstitial fibrosis exceeding 50% in 10 patients (14%) (Figure 1).

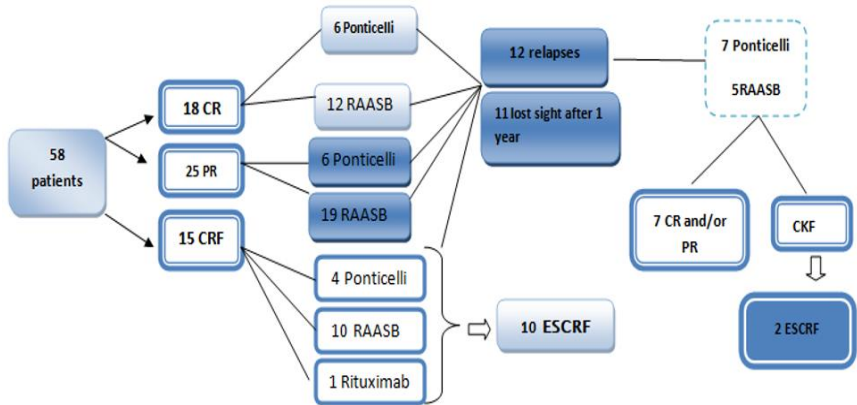
**Table 1: biological profile of patients at the admission**

Variable	Mean	Standard deviation
Proteinuria (g/day)	9.1	4.21
Protidemia (g/l)	48.8	10.7
Albuminemia (g/l)	25.2	11.6
Urea (g/l)	0.76	1.29
Serum creatinine (mg/l)	22.8	-
eGFR (mL/min)	82.4	-
Hémoglobin (g/l)	12.1	2.99
Cholesterol (g/l)	2.51	0.89
Triglyceride (g/l)	1.95	0.99

eGFR : estimated glomerular filtration rate; PU : proteinuria; g: gramme; l: litre; min minute.

MN was secondary in 13 (18.3%); the etiologies were infectious (05 cases), autoimmune (05 cases) and neoplastic in 03 cases. Fifty eight patients (81.6%) had idiopathic MN; they all received treatment with RAAS blockers for 6 months. Twenty-three of them subsequently received immunosuppressive therapy (17 according to the classical Ponticelli protocol and 6 according to the modified Ponticelli protocol). Only one patient received anti-CD20 therapy.

After a mean follow-up of 8.4 months, 18 patients (31%) were in complete remission and 25 (43.1%) in partial remission. Five patients (8.6%) were in chronic renal failure with a mean creatinine level of 411 μmol/l and 10 (11.7%) were in chronic renal failure. Twelve patients presented a relapse after a mean delay of 20 months; 7 of them were treated according to the classic Ponticelli protocol (Figure 1)



**Figure 1: Evolution of primary membranous nephropathy in our series**

**CR:** complete remission, **PR:** partial remission, **RAASB:** renin angiotensin aldosterone system blockers, **ESCRf:** end-stage chronic renal failure, **CKF:** chronic kidney failure

The predictive factors for progression to chronic renal failure in our study were: the existence of renal failure at the time of diagnosis (p=0.001) and the

presence of tubulointerstitial damage >50% on kidney biopsy (p=0.0041) (**Table 2**).

**Table 2: Predictive factors of end stage renal failure in patients with MN**

Variable	Complete remission (n=18)	Partial remission (n=25)	Chronic renal failure (n=15)	p
Age > 50 years	3(15.8)	8(42.1)	8 (42.1)	0.082
Male gender	5(18.5)	15 (55.6)	7(25.9)	0.11
Proteinuria (PU) > 5g/day	11 (33.3)	15(45.5)	7(21.2)	0.64
Renal failure at admission	0(0)	9 (45)	11 (55)	<b>0.001</b>
Ponticelli protocol	6 (27.3)	12(54.5)	4(18.2)	0.35
Tubulo-interstitial lesions > 50%	2(15.4)	4(30.8)	7(53.8)	<b>0.041</b>

## DISCUSSION

Primary membranous nephropathy (MN) is the most common cause of adult nephrotic syndrome (NS), reaching 20 to 37% of cases [1,2]. Its incidence remains difficult to specify since approximately 25% of patients have asymptomatic proteinuria (PU) [3]. In our department, MN represented 11.2% of all kidney biopsies.

The disease affects men preferentially with a sex ratio of 2.1 [4]. It may occur at all ages with a peak incidence between 30 and 50 years [4], which is consistent with the results of our series where the average age at diagnosis was 43.5 years old.

According to the literature, the onset of the disease is almost always insidious [6]. Glomerular proteinuria is the predominant biological sign; depending on the series, 7 to 54% of patients have asymptomatic proteinuria but in 40 to 80% of cases, the disease presents with a nephrotic syndrome [4, 7,8]. We reported in our series an average 24 hours proteinuria of  $9.1 \pm 4.21$  g/24 hours. Microscopic haematuria is noted in approximately 25 to 85% of cases [7,8]. Arterial hypertension is reported in a very variable way [7- 9]; it was observed in 20% of our patients. If the presence of renal insufficiency is

rarely the revealing sign of the disease in the literature [10], 33.8% of the patients in our series were in renal insufficiency at the admission.

The histology allows the positive diagnosis of the disease. MN is characterized by lesions that vary over time, reflecting an evolving process. According to the literature, stage I and II of MN are the most frequent, found respectively in 55% and 37.5% of cases according to the Aden study [7]. In our study, stage II of MN was prominent (59.2%), while stages I, III, and IV were respectively found in 22.5%, 1.4%, and 16.9% of cases.

The predominant immunoglobulin (Ig) on immunofluorescence (IF) is IgG, whose subclasses can inform the pathologist: IgG subclasses 2 and 3 are found in secondary MN (tumors, lupus), while IgG subclasses 1 and 4 are found in idiopathic MN. The infiltration of the glomeruli by neutrophils (8 neutrophils/glomerulus) also helps to differentiate between primary and secondary forms of MN [10].

In 20% of cases, MN complicates or precedes the evolution of an autoimmune or neoplastic condition, an infectious disease or a drug medication. If the etiological investigation is negative (80% of cases approximately), MN is said to be primary. In our series, secondary MN of autoimmune and infectious

causes were prominent: lupus membranous nephropathy was found in 4 patients (30.7% of secondary forms) and neoplastic pathology was objectified in 3 patients (23%). Our results are different from those found in the series of Zeng et al [7] and Aden et al [8] where autoimmune and infectious causes represented respectively 50% and 12% of secondary causes of MN. An association of MN with different types of solid tumors is reported; Lefaucheur et al [11] reported an incidence of 10% of cancer, with a predominance of prostate and lung cancers.

Despite numerous studies and because of the 30% spontaneous remission rate, the value of specific immunosuppressive treatments for primary MN remains debated. It is accepted that immunosuppressive treatment should be considered only after 6 months of disease progression on blockers of renin angiotensin aldosterone system, except in patients with rapid deterioration of Renal Function and/or persistent NS [11]. Immunosuppressive therapy is indicated after 6 months of nephroprotection [12]. The most widely studied treatments for primary MN are alkylating agents (such as cyclophosphamide), calcineurin inhibitors (such as cyclosporine and tacrolimus), mycophenolate mofetil (MMF), rituximab, and intravenous Ig [13].

The efficacy of treatment with corticosteroids alone is not convincing [14]. Prospective randomized studies have shown that the combination of alternating corticosteroid therapy with an alkylating immunosuppressant provides a significant improvement in renal prognosis [15]. Subsequently, calcineurin inhibitors have been used and have shown significant efficacy in terms of remission of SN (70-80% partial or complete remissions) with acceptable tolerability. However, the recurrence rate after the discontinuation of treatment is more than 50% [16, 17] and prolonged treatment with calcineurin inhibitors exposes the patient to a risk of renal fibrose. MMF has not been extensively studied and the published results for this type of treatment are not convincing [18]. Recent randomized controlled studies [16, 19] have shown the superiority of rituximab monotherapy with good tolerance and significant efficacy in achieving remission of NS.

The concentration of PLA2R antibody appears to be associated with response to treatment and seems to be an early predictive of MN relapse [20]. When immunosuppressive therapy is indicated, it seems reasonable to suggest regular and progressively spaced measurement of PLA2R antibody during the first 2 years of follow-up of primary MN with initial positive anti PLA2R antibody [21]. A high antibody level is likely to be a poor prognostic factor and may

reflect the immunological activity of the disease [22].

Given the variability in the course of MN, 15 to 30% of cases progress to spontaneous remission and one-third of cases progress to chronic renal failure. In our series, 43 patients (74%) were in remission with complete remission in 18 patients (41.8%) after a mean duration of 8.4 months, and partial remission in 25 patients (58.1%). These results are in concordance with the literature. In Shippelli et al series [23], 5 to 20% of patients were in complete remission at 10 years, 25 to 50% in partial remission with one or more relapses of the disease, and 10 to 25% in end-stage chronic renal failure. The latter is influenced by several prognostic factors, including gender, age, proteinuria, whether remission is achieved, and renal histological lesions [22, 24- 26]. The predictive factors for progression to chronic renal failure in our study were: the existence of renal failure at the time of diagnosis and the presence of tubulointerstitial damage >50% on kidney biopsy. These results are consistent with those found in the study of K. Dahon et al. [26] which showed that the presence of significant interstitial fibrosis, low creatinine clearance on admission, and proteinuria output >5g/24hours were associated with the development of chronic renal failure. In the study by Schieppati et al [23], male gender and age >50 years were the only significant prognostic factors.

## CONCLUSION

Membranous nephropathy is the main cause of nephrotic syndrome (NS) in adults. According to our study, primary MN is the most frequent in Morocco. Third of the patients in our series were in renal insufficiency at the admission. Renal failure on admission and the presence of interstitial fibrosis exceeding 50% seems to be the factors of poor renal prognosis in Moroccan patients.

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