Iranian Journal of Pathology (2006)1 (2), 69-74

Original Article

Clinicopathologic features and outcome of membranous nephropathy in Markaz Tebi children hospital

Nakysa Hooman[1], Seyed Taher Esfehani[2], Abas Madani[2], Esfandiar Bodagi[3], Parvin Mohseni[2]

1. Department of Internal Medicine and Nephrology, Ali Asgar Children Hospital, Tehran
2. Department of Internal Medicine and Nephrology, Hasan Ahari Children Hospital, Tehran
3. Department of Internal Medicine and Nephrology, Tous Hospital, Tehran

ABSTRACT

Background and Objectives: **This research study was conducted to determine the correlation between the clinicopathologic features and the outcome of membranous nephropathy.**

Materials and Methods: **Data were retrospectively reviewed from all patients with a diagnosis of membranous nephropathy. Demographic, initial laboratory, and clinical findings were collected and the biopsy specimens were reviewed to classify them. To compare means, frequency, and to find correlation, student t-test, non-parametric χ^2 and Kendall-tau statistical tests were used respectively. A p value less than 0.05 were considered significant.**

Results: **It was found out that during the years 1972-1996, 72 out of 2118 kidney biopsies had been diagnosed as membranous nephropathy. In this respect, male/female ratio was 2:1 (with a range of 1.5-14 years). Meanwhile, 45 out of 72 cases were idiopathic membranous nephropathy (IMN). Furthermore, 27 out of 72 had a secondary cause of the disease due to systemic lupus erythematosus (11 cases) and HBsAg positive (12 patients). The most common features in both groups were nephrotic syndrome and hematuria. In idiopathic and in chronic renal failure groups, remission occurred in 20.9% and 20.9 % of the cases respectively during an averaged 2.13 years of follow up. The statistical test Kendall-tau was used to determine the correlation between initial findings and outcome in IMN. In this regard, a significant direct correlation was found between progression to renal failure and proteinuria (p = 0.009) and/or age (p = 0.01) at the time of admission. For secondary membranous nephropathy, the outcomes were variable depending on the etiology.**

Conclusion: **Proteinuria, age, and underlying etiology are the most important factors determining the renal outcome in membranous nephropathy.**

Key words: **Idiopathic Membranous Nephropathy, Hepatitis B, Systemic Lupus Erythematosus**

Received: 25 February 2006
Accepted: 11 May 2006
**Address communications to: Dr. Nakysa Hooman, Ali Asgar Children Hospital, Vahid Dasgerdi St., Modares Highway, Tehran-Iran*
E-mail:nakisa45@yahoo.com

Introduction

In membranous nephropathy (MN), the pathological process continues in a progressive fashion and may be diagnosed during evaluation of asymptomatic proteinuria or nephrotic syndrome. MN is divided into idiopathic (IMN) and secondary groups. The prevalence of idiopathic MN is estimated between 1-6% (1). Chronic renal failure develops in 18% of children. The relationship between gender, age, hypertension, proteinuria, pathological staging of IMN, and prognosis has been controversially reported (1-12). Secondary MN is associated with systemic lupus erythematosus, hepatitis B, drugs and so forth (1). Currently, no definitive treatment is available for children and most studies are limited to adults (1, 2, 4, 13-17). Prevalence, etiology and clinical presentation of Iranian children with MN have not yet been reported in details.

Materials and Methods

Data were retrospectively reviewed from all patients (admitted to Markaz Tebi Children Hospital, Tehran) with a diagnosis of membranous nephropathy from 1972 to 1996. Demographic, initial laboratory, and clinical findings were collected and the biopsy specimens were reviewed to classify them by three separate pediatric nephrologists. The renal specimens were prepared for light and immunoflourescent studies. The light microscopic preparations were cut at 4 micrometer thickness, stained with Hematoxylin and eosin, periodic acid Schiff, Masson trichrome, and silver stain. For immunoflourescent studies, tissue sections were stained with antisera to IgG, IgA, IgM, fibrin, C3, C4, and C1q. Histological classification according to Ehrenreich and Churg (18) was used to place the biopsy findings into stages I to IV. Urinary protein excretion>4 mg/m2/h and >40 mg/m2 /h were defined as proteinuria and nephrotic range proteinuria respectively. Hematuria was defined as more than five red blood cells per high power field in the sediment of 10 ml centrifuged fresh urine of two specimens. Blood pressure more than 95% for age and height was considered hypertensive. Remission was defined as absence of edema, proteinuria, hemauria, and return of serum albumin concentration to normal values with normal glomerular filtration rate. Creatinine clearance less than 80 ml/min was considered as renal failure. The patients with inadequate laboratory tests were excluded from the study. To compare means, frequency, and to find correlation, student t-test, non-parametric χ^2 and Kendall-tau statistical tests were used respectively. A p value less than 0.05 were considered significant.

Results

It was found out that 72 out of 2118 renal biopsies have a diagnosis of MN. The average of age (± SD) was 7.9 (± 3.6) years (with a range of 1.5–14 years). Meanwhile, 22 cases were under 5 years (19 males , 3 females) , 29 were from 5 to 10 years (19 males, 10 females) and 21 patients were over 10 years (12 males, 9 females). These differences were statistically significant (χ^2, p=0.03). In addition, the total was 49 males and 24 females.

The common presentations and their frequency were as follows: 89% had proteinuria (73.6% of them with nephrotic range proteniuria), 76.4% had hematuria (11% of them with gross hematuria), 83.3% with edema, and cases with rare findings including hypertension (22%), hepatomegaly (19.6%), acute renal failure (14%), and deep vein thrombosis (1.38%). According to clinical and laboratory findings, 45 out of 72 cases had idiopathic MN (62.5 %). Meanwhile, one of them had hereditary C4 deficiency. In addition, 27 out of them were considered secondary due to SLE (11 cases), hepatitis B (12 patients), D-penicillamin (1 patient), rheumatoid arthritis (1 patient), alopecia areata (1 case), and tuberculosis (1 case). Using ANOVA and Chi square statistical tests, the proportion of sex and age groups was different for each etiology. Furthermore, MN was more common in males and comprised the main gender in hepatitis B groups; however, SLE was

slightly more frequent in females. This difference was statistically significant (p = 0.03). Regarding age, MN was observed more frequently in children older than 5 years but hepatitis B group was much younger than the other groups. This differences was also significant (p = 0.013).

After 25 months of follow up in this study, it was obtained that in average (12-120 months) 28% of the total group achieved remission, 55% had persistent proteinuria, and 17% progressed to chronic renal inadequacy. Remission was seen more frequently in hepatitis B group (60%), whereas persistent proteinuria was more common in SLE group (73%) and the percentage of chronic renal failure was higher in IMN group (21%). Using Jonckheere-Trepsta test we found only a significant correlation between outcome, age (p = 0.014), and proteinuria (p = 0.008). Sex, hypertension, hematuria, and initial serum creatinine had no significant influence on outcome (p>0.05).

Figure 1 shows pathological classification and initial presentation of IMN. There was no correlation between pathological classification and initial presentation of IMN (p>0.05).

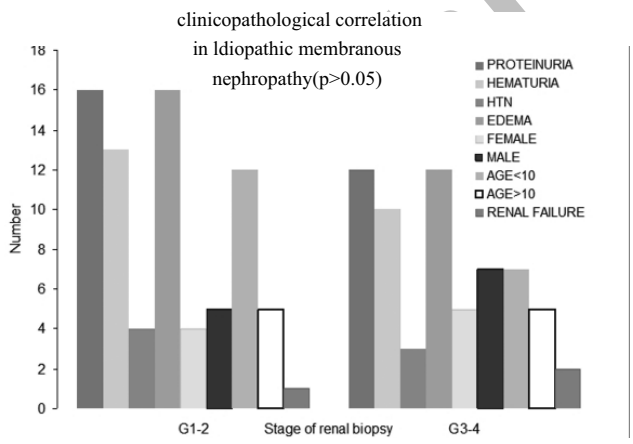

Figure 1: pathological classification and initial presentation of IMN

Using Ehrenreich and Churg classification, 20% of them were at stage I, 40% classified as stage II, 34% was stage III, and stage IV comprised 6% of patients (Figure 2).

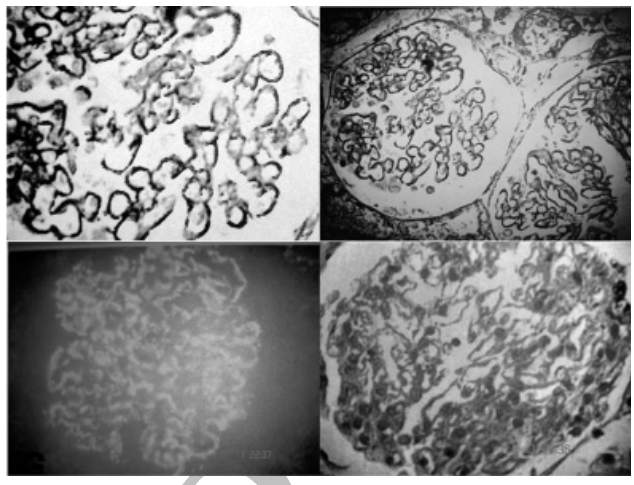

Figure 2: [Top] Thick basement membrane of glomeruli and subepithelial spikes on light microscopy (Reticulin X100 left – X40 Right), [Bottom right] capillary wall are thickened and cellularity is normal (H&E X40), [Bottom left] Granular subepithelial deposit of IgG on Immunoflurecent.

We also found no correlation between stage of renal biopsy and initial clinical features, laboratory findings, and renal outcome of IMN (p>0.05).

Discussion

Several factors including age at time of presentation, gender, hypertension, degree of proteinuria, and pathological staging have been considered important in determining the prognosis of IMN in children, but the existing data in this field are limited due to rarity of MN in children (1,3-6, 8-10, 12, 16). In this study, only severity of proteinuria and onset age had adverse effects on outcome. Meanwhile, it has been reported that 25% of patients with nephrotic syndrome progress to chronic renal failure (13). Corticosteroids, cytotoxins, antioxidants, ACEI, angiotensin II blockers, and IVIG are used to treat these patients, but the obtained results are not conclusive (1-2, 13, 15, 16). The rarity of disease in children eliminated the need to perform a controlled trial. Membranous nephropathy is rarely seen in pediatric clinics. The prevalence of MN was 3.4% in this study. More than half of the

patients were under 10 years and male to female ratio was 2:1. A survey of the literature shows the same result (1, 7, 9-10, 12).

The most common presentations were nephrotic syndrome with hematuria. Isolated hematuria and hypertension were less common. These results were the same as the other studies (1, 4-10, 12). In a study conducted in France (19), the isolated proteinuria was reported in 56% of cases. This figure was higher than our results. This difference is probably due to screening asymptomatic proteinuria by urinary analysis. In addition, 52% of cases had IMN and 47% had associated conditions that included SLE (22%) and HBV (20%). Drugs, infectious conditions, and other collagen vascular diseases comprised 5% of cases. The distribution of etiology has been the same in literature and neoplasm, autoimmune disorders, infectious disease, drugs, and heavy metals are also reported as etiologic factors (1, 4, 7, 11-12). We also found four cases due to D penicillamin, tuberculosis, rheumatoid arthritis, and alopecia areata. In this respect, MN due to rheumatoid arthritis has been reported after treatment by gold or D-penicillamin, but there are some reports of MN following rheumatoid arthritis with no history of drug exposure (20-21). Our patients had the same condition.

In Africa, China, and Greece, hepatitis B is a significant factor in the etiology of MN. Those who have received α-interferon show a higher percentage of remission and after steroid administration, recurrent relapses were observed (1, 14, 22-23). In this study, more than half of the patients suffered from hepatitis achieved remission and only 10% progressed to chronic renal failure. Children with SLE remained proteinuric during follow up and renal failure was seen only in 9% of cases as compared to 20.9 % in IMN. Survey of literature showed the same result (1, 11, 17). It is obvious that progression to renal inadequacy was higher in idiopathic group as compared to secondary group. We found the adverse effect of proteinuria on kidney outcome, so intensive treatment of proteinuria in children with MN may improve the survival of renal function.

Conclusion

proteinuria, age, and underlying etiology are the most important factors determining the renal outcome in membranous nephropathy.

References

1. Makker SP, Membranous nephropathy. In: Avner ED, Harmon WE, Niaudet P, eds. Pediatric nephrology, 5th ed, Philadelphia : Lippincott Williams & Wilkins, 2004 641-654

2. du Buf-Vereijken PWG, Branten AJW, Wetzels JFM.Idiopathic membranous nephropathy: outline and rationale of a treatment strategy. Am J Kidney Dis 2005 46: 1012-1029

3. Yoshimoto K, Yokoyama H, Wada T, et al. Pathologic findings of initial biopsies reflect the outcomes of membranous nephropathy. Kidney Int 2004 66 (1): 464-465

4. Passos EM, Legallicier B, and Godin M. Membranous nephropathy. Rev Prat 2003 53 (18): 2033-2038.

5. O'Callaghan CA, Hicks J , Doll H, Sacks SH, Cameron JS. Characteristics and outcome of membranous nephropathy in older patients. Int Urol Nephrol 2002 33 (1): 157-165.

6. Toth T and Takebayashi S, Idiopathic membranous glomerulonephritis: a clinicopathologic and quantitative morphometric study. Clin Nephrol, 1992. 38 (1): 14-19

7. Locard-Bisot S, Cochat P, Gilly J, et al. Membranous glomerulonephritis in children: 20 cases. Pediatric 1990 45(7-8): 527-532

8. Donadio JV Jr, Torres VE, Velosa JA, et al. Idiopathic membranous nephropathy: the natural history of untreated patients. Kidney Int 1988 33(3): 708-715

9. Ramirez F, Brouhard BH, Travis LB, Ellis EN. Idiopathic membranous nephropathy in children. J Pediatr 1982 101(5): 677-681.

10. Latham P, Poucell S, Koresaar A, Arbus G, Baumal R. Idiopathic membranous glomerulopathy in Canadian children: a clinicopathologic study. J Pediatr 1982 101(5): 682-685

11. Donadio JV Jr, Burgess JH, and Holley KE. Membranous lupus nephropathy: a clinicopathologic study. Medicine (Baltimore) 1977 56(6): 527-536

12. Habib R, Kleinknecht C, and Gubler MC.

Extramembranous glomerulonephritis in children:report of 50 cases. J Pediatr 1973 82: 754-766

13. Makker SP. Treatment of membranous nephropathy in children. Semin Nephrol 2003 23(4): 379-385

14. Sithebe NP, Kramvis A, Kew MC, Bhimma R, Coovadia HM, Naidoo P.Hepatitis B and C virus co-infection in black children with membranous nephropathy. Pediatr Nephrol 2002 17(8): 689-694

15. Haas M, Mayer G, Wirnsberger G. Antioxidant treatment of therapy-resistant idiopathic membranous nephropathy with probucol: a pilot study. Wien Klin Wochenschr 2002 114(4): 143-147

16. Yoshimoto K, Yokoyama H, Wada T. The short- and long-term outcomes of membranous nephropathy treated with intravenous immune globulin therapy. Nephrol Dial Transplant 1999 14: 2379-2386

17. Southwest. Pediatric Nephrology Study Group, Comparison of idiopathic and systemic lupus erythematosus associated membranous glomerulonephritis in children. Am J Kidney Dis 1986 7: 115-124

18. Schwartz MM. Membranous glomerulonephritis. In: Heptinstall RH, ed. Pathology of the kidney , 4 ed.Vol. 1. Boston: Little,Brown and Company ; 1992 559-626.

19. Simon P, Ramee MP, Autuly V, et .al. Epidemiology of primary glomerular disease in a French region, variations according to the period and age. Kidney Int 1994 46(41192-1198

20. Helin HJ, Korpela MM, Mustonen JT, Pasternack AI. Renal biopsy findings and clinicopathologicalal correlation in rheumatoid arthritis. Arthritis Rheum 1995 38(2): 242 - 247

21. Nakono M, In HI, and Saito T. Renal disorders in rheumatoid arthritis. Nippon - Rinsho 1992 50(3): 576-580

22. Lin CY. Treatment of hepatitis B virus associated membranous nephropathy with recombinnt alpha-interferon. Kidney Int 1995 47(1): 225-230

23. Gilbert RD and Wiggelinkhuizen J. The clinical courses of hepatitis B virus assoiated nephropathy. Pediatr Nephrol 1994 8(1): 11-14