Clinicopathological Correlation in 100 Patients With Membranous Nephropathy

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J Fac Med Baghdad
2005; Vol. 47, No.4
Received Jan. 2004
Accepted March 2004

Summary:

Background: *Membranous nephropathy is a glomerular disease characterized clinically by proteinuria. The morphological identification of membranous lesion is the first step towards a final diagnosis and there are no reliable morphological methods for differentiation between primary and secondary forms of MN.*
Objective: *the disease appears to have an immunological basic and immunosuppressionhas has been used with some benefit. Diagnosis at an early stage can differentiate between patients who might benefit from treatment and those unlikely to benefit.*
Subject & method: *1250 kidney biopsies were reviewed from (January 1982 - January 2003) at the nephrology unit - Rasheed Hospital Baghdad Iraq. Only 100 patients proved to have membranous nephropathy. Patients' age ranged from 1 0 - 6 0 years. 82 were males 18 were females. 55 of the 100 patients presented as nephrotic syndrome (NS), and 43 as isolated proteinuria. The other two patients, one had microscopical hematuria and the other had chronic renal failure*
Results: *membranous nephropathy is a less common cause of nephrotic syndrome in children, adolescents, and adults below 30 years of age.*
Conclusion: *on clinical ground, it is very difficult to distinguish membranous nephropathy from minimal change disease.*
*keywords * renal biopsy . proteinuria*

Introduction:-

Me'mbranous nephropathy is a glomerular disease that is clinically characterized by proteinuria. In many series, it is the most common glomerular disease underlying nephrotic syndrome in adults. Historically, accurate definition of MN awaited the development of sensitive histological techniques, since the pathology is far more specific than clinical the picture [1]. In 1930s Belf[2] and Dunn[3] noted thickening of glomerular capillary walls in many nephrotic patients but their techniques did not allow them to discern the cause of thickening nor to distinguish mild membranous changes from lipoid nephrosis[4]. The introduction of silver tissue staining, electron microscopy, and immunoflorescent [5]. had shown that MN is a morphological pattern of diverse etiology. A large number of associated or precipitating factors have been identified in individual cases, but no cause can be identified. The glomerular changes consist of varying degree of glomerular basement reaction to subepithelial deposits. The morphological identification of membranous lesion is the first step toward a final diagnosis and there are no reliable morphological methods for differentiation between primary and secondary form of MN[6]. MN is most common in the fifth to seventh decades but occurs at all ages with male predominance 2-3/1. Initial presentation is invariably with signs of altered glomerular permeability, 70-80% of patients having NS at onset, and the remainders are referred for investigation of proteinuria.

In renal biopsy series, MN is found in 20-30% of nephrotic adults, and in 1-9% of nephrotic children. The wide range of the figures in nephrotic children probably reflects difference in referral and selection for biopsy rather than a real variation in true incidence, which is likely to be in the region of 1%[7]. Proteinuria may be highly selective especially in early lesions and it is of little diagnostic value. Microscopic hematuria is detectable in most patients, but microscopic hematuria and other nephrotic features are rare[8,9].

In the absence of systemic manifestations, other investigations do not usually contribute to the diagnosis. Some patients, however, appear to be in a grey area between idiopathic and lupus MN[1]. The presence of hypocomplementemia may point to an early presentation of lupus since serum complement value is normal in idiopathic MN, and recent reports suggested that presence of terminal complement complex (C5b-9) as a dynamic marker of ongoing immunological injury and may be useful in the initial

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assessment and monitoring of patients with idiopathic MN, and in identifying patients who may derive benefit from immunosuppressive therapy[1m].

Hypertension may be present at the onset of the disease or may develop at sometime during its course in up to half of the patients. Most patients with idiopathic MN have benign course but a minority develop severe persistent NS or end stage renal failure (ESRF). The disease appears to have an immunological basis, and immunosuppression has been used with some benefit. An early diagnosis is important [112].to differentiate patients who might benefit from immunosuppression.

PATIENTS AND METHODS:

This retrospective and prospective study is based on 1250 patients examined by renal biopsy at department of nephrology AL-Rasheed Hospital Baghdad - Iraq between 1981 and 2003.

Renal tissue was obtained by percutaneous biopsy using modified menghini surecut. Two pieces were obtained and sent to two histopathologists. All specimen slides were stained with haematoxilin and eosin (H&E), PAS and silver impregnated and examined by light microscopy (LM). Patient's age ranged from 10-65 years. 900 were males and 350 were females. Of those only 100 patients had biopsy proven MN, 82 were males and 18 females. Careful search to define all probable or possible causes for secondary MN was carried out. HBsAg were done for 50 patients & HCV anti-bodies for 30 patients, and collagen survey including ANA, Anti double stranded DNA, Rheumatoid factor and C3 - C4 complement were done for 60 patients. VDRL was done for 30 patients and serum cholesterol and blood sugar for all patients. Nephrotic syndrome was considered to be present when urine protein excretion was 3.0 gm/ 24 hours or more and serum albumin concentration was below 3.0 gm/ dl. Proteinuria was defined as urine protein excretion of 200mg/ 24 hrs or more but still not sufficient to cause NS. Hematuria was present when three or more red blood cells per high power field in an ordinary sediment count. Renal function was determined by blood urea (normal 10-20mg/dl), serum creatinine concentration (normal 1.5mg/dl) and creatinine clearance (normal 90-130ml/ minute/ 1.73m^2. Chronic renal failure was defined by persistent rise in serum creatinine more than 1.5mg/dl and creatinine clearance less than 60ml/ minute / 1.73m" . Hypertension was present when the blood pressure was over 160/95 mmHg or when the patient was receiving anti-hypertensive medication.

RESULTS:

The clinical findings of the study population are presented in table(l). Of the (100) patients with MN82 were males and 18 were females with mean age of31 years. Fifty- five from the l00 patients had N.S at the time of presentation, and 40 from the 55 patients had edema and NS was the presenting symptom whereas the remaining 15 patients had heavy proteinuria associated with hypoalbuminemia but had no edema. Proteinuria was present in 43 patients. Macroscopical haematuria was the presenting feature in one patient while microscopical haematuria presented in 29 patients. Chronic renal failure (CRF) was the presenting feature in one patient. Blood pressure at onset of diagnosis was normal in (77) patients. Coexistent disease possibly related to MN included 10 patients with diabetes mellitus but only one patient had diabetic retinopathy and arteriolar changes typical of diabetic nephropathy in kidney biopsy. Two patients, both of them were from south of Iraq, gave history of schistosmiasis. One clinically presented with haematuria of one-year duration & the other with NS and haematuria of one month duration. One 42 years male patient had Hashimotos hypothyrodism, diabetes mellitus-type II, hepatitis, but HBsAg was negative. The presenting feature of this patient was proteinuria of 2 years duration. The results of other investigations are shown in the table *2.* Nine male patients had HBsAg positive, and 3 of them had history of war injury and received frequent blood transfusions. Five patients had positive antinuclear antibody (ANA); 4 were females & one was male. One patient had psoriasis & he was on methotrexate.

Eighty patients had hypercholestremia ranging from 250 -550mg/dl, and 40 of them clinically presented with NS.

DISCUSSION:

In our series, MN was detected after the age of 31 years with male predominance, 5:1 ratio. This age and sex frequency closely agrees with the experience of others who reported fairly large series of patients with MN, and whose pathological criteria for diagnosis are clearly defined and correspond to those in our report. In our series, the sex ratio was high for males because we were dealing with patients in the military service. The mean age for the 1250 patients was 25 year but our patients had MN at a mean age of 31 years, which supports the result of other reports where MN occurs most commonly in adults between 30 and 50 years of age but also occurs in childhood and old age [(1)] Other reports in the American literature confirmed the rare occurrence in children. Habib and Royer had studied a series of 37 children with MN at the Hospital-De-Enfants-Maladies-in Paris suggested that age frequency may vary geographically [(114,13,16)]

The frequency of NS in our series is 55 percent, which is consistent with most reported series (Row et al 1975 Ramazy et al 1981) In contrast, only 8 percent of 260 patients with MN described by Bergianal (1974) showed that the mean age for NS and the mean age was under 30 years [(]. Hypertension was found in

33% of patients when MN was diagnosed, Gluick et al (1973) [16]. Hypertension may develop at sometime during the course of disease in half of the patients"*. One patient in our series showed impairment of renal function, which is lower than in the series reported by Honkane et al where 5 from 67 patients had impairment of the renal function. Sixteen patients had proteinuria at the time of presentation (43%), but the NS commonly develops at sometime during evolution of the disease. Although proteimuria generally tends to diminish with progression of glomerular lesion[11] recent studies suggest that proteinuria may be involved in pathogenesis of accompanying tubulointerstitial lesion. Coexistent diseases, possibly related to MN, were found in two patients who gave history of schistosmiasis, and this was consistent with discovery of some infectious antigens in glomeruli of patients with MN [19]. The associated systemic infection included quatrain malaria, schistosomiasis- leprosy, syphilis, hydatid disease, scabies, thread worm and rectal abscess[1]: U', but the most frequently reported associated infection is hepatitis[120], mainly hepatitis B in children. 21 of 98 children biopsied for glomerular disease had MN associated with hepatitis[20] In our study 9 of 50 patients with MN had HBsAg +ve and only one of them presented with NS. As reported in other series 30-40% of patients in Asia to less than 1% in the U.S.A [21].5 of 60 patients ANA were positive two of them were females with diagnosis of rheumatoid arthritis and specific treatment in form of gold therapy. No example of familial MN observed reported in our patients. Barite and associates observed reversal of basement membrane abnormality in five patients with remission of NS [22]. To assess of the prognosis of given patients with remission disease is of the idiopathic or secondary variety in some instance of the secondary MN the identification and elimination of specific antigen can cure the disease

Table 1

Clinical finding in patients with MN	
• No. of patients	100
• M/F	82/18
• Mean age years	31
Clinical presentation	
• NS	55
• Proteinuria	43
• Hematuria	1
• CRF	1
Additional mode of presentation	
• Hematuria with NS	29
• Hypertension	33
• S. cr > 1.5 mg/dl	22
• S. cr < 1.5 mg/dl	78

Investigation	No of pt	+ve	Male	Female
HBsAg	50	9	8	1
HCVAb	50		-	-
ANA	60	5	1	4
Anti Ds DNA	60	-	-	-
C 3 - C 4	60	Normal	Normal	Normal
VDRL	30	2	2	-

CONCLUSION:

MN is not a common cause of nephrotic syndrome in children, adolescents, and adults below the age of 30 years.

Early in the course of the disease it is difficult to distinguish MN at the time of presentation from minimal change disease on clinical ground alone. *The* Incidence and prevalence of MN are impossible to quantitate. -Hepatitis B virus is the most common associated infectious disease.

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