Assessment of Treatment Response of Iraqi Patients with Membranoproliferative Glomerulonephritis with Emphasis on Renal Function and Proteinuria Regression

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Abstract

Background: Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury with characteristic light microscopic changes. It can be primary idiopathic renal disease or secondary to chronic infections, autoimmune diseases and complements dysregulation.

Objective: To evaluate treatment response in a group of patients with MPGN regarding renal function and proteinuria regression.

Patient and Methods: Thirty three adult patients with MPGN (above the age of 18 years) were included in the study. Males were 19 and females were 14. All patients were followed up for two years. Laboratory investigations included complete blood counts, urine examination, renal function test, lipid profile, virology screen (hepatitis B virus and hepatitis C virus), collagen diseases screen (antinuclear Ab, anti double stranded DNA, extractable nuclear antigens, complements C3 and C4), also screening for multiple myeloma was done with serum protein electrophoresis and urine bence jones protein. All patients were given standard form of treatment (Anti platelets, statins, diuretics, angiotensin converting enzyme inhibitors/angiotensin receptor blockers), some patients were given steroids, others, immunosuppressive drugs.Their responses to treatment were studied and compared.

Results: The cause of MPGN in this study was idiopathic in twenty six patients (79%). It was secondary to HBV, HCV, and systemic lupus erythematosus in seven patients (21%). Four (58%) out of seven patients with normal RFT have partial response to steroid therapy and they showed decreased proteinuria. The remaining three (42%) patients showed no response. Two Patients with normal RFT who received mycophenolate mofetil, responds by decreasing their proteinuria to less than 1 g / 24h. nine patients with impaired RFT received steroid treatment only or steroid plus MMF, four (44%) patients have stabilized renal function, the remaining five (56%) patients had progressive decline in renal function. Three patients with HBV infection who were given alfa interferon or lamivudine showed stabilized RFT and decreased proteinuria. One patient with HCV infection showed progressive decline in renal function, he was maintained on standard treatment only. Two patients with SLE and impaired RFT were given cyclophosphamide and steroid, their RFT stabilized during the follow up period

Conclusion: Patients who presents with normal RFT have better response to treatment. Than patients who presents with impaired RFT. Also patients with secondary MPGN (HBV and SLE) have responded at least partially to antiviral and /or immunosuppressive therapy.

Key words: Membranoproliferative, glomerulonephritis, proteinuria, renal function

Received: 7th April 2015

Accepted: 20th April 2015

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Introduction

Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury with characteristic light microscopic changes that is characterized by mesangial hypercellularity, endocapillary proliferation, and double-contour formation along the glomerular capillary walls [1]. In patients with active disease, the urine sediment reveals hematuria, and occasionally with red cell casts. There is a variable degree of proteinuria; and the serum creatinine may be normal or elevated. Hypocomplementemia is common in all types of MPGN [2-6].

Membranoproliferative glomerulonephritis was initially classified into three categories: types I, type II and type III based upon the location of immune deposits in the mesangium, subendothelial and subepithelial space) [1-6].

Recently MPGN is classified as being mediated by immune complexes, by complement dysregulation that leads to persistent activation of the alternative complement pathway, or rarely, by mechanisms not involving immunoglobulin or complement deposition, such as endothelial injury [7].

These disorders can be distinguished by Immunofluoresence microscopy (IF) [8-9]. Immune complex-mediated MPGN results from chronic antigenemia and/or circulating immune complexes and can be seen in chronic infections (most commonly secondary to chronic HBV and HCV), autoimmune diseases (e.g.SLE), and monoclonal gammopathies (e.g. multiple myeloma)[10-17]. Complement-mediated MPGN results from dysregulation and persistent activation of the alternative complement pathway. Immunofluoresence microscopy of kidney sections demonstrates C3 staining, but no significant immunoglobulin staining [3].

Complement-mediated MPGN may be further classified based upon ultra-structural features observed on EM as Dense deposit disease or complement-3 glomerulonephritis (C3 GN) [6-7].

Traditionally, two forms of therapy, steroids and anti-platelets drugs have been evaluated in patients with idiopathic MPGM who are at risk of progressive disease. Unfortunately these studies are generally flawed due to lack of control or the use of retrospective controls. Furthermore they were performed prior to the establishment of association between MPGN and hepatitis virus infection, in patients with seemingly idiopathic MPGN [19].

There has been no systemic evaluation of steroid treatment in idiopathic MPGN in adults. Retrospective studies have not shown any clear benefit of steroid treatment, although treatment was not as prolonged as in children [21, 22, 23].

There are only limited data on the use of cytotoxic and other immunosuppressive drugs in MPGN [26].

The aim of this study is to evaluate treatment response in a group of patients with MPGN regarding renal function and proteinuria regression.

Patient and Methods

Thirty three adult patients with proteinuria in whom renal biopsy confirmed the histological diagnosis of MPGN were involved. All the patients were followed up for at least two years. Patients were gathered from the nephrology division at Al-Khadumyia teaching hospital, during the period from July 2004 to July 2007.

The inclusion criteria in this study were: adults above the age of 18 years with a renal biopsy of MPGN. Younger patients were excluded.

A detailed history and physical examination, with laboratory investigation,

and sonography were recorded in special forms.

Laboratory investigations included: Twenty four hour urine collection for protein and creatinine clearance, general urine examination, complete blood counts and ESR, blood urea, serum creatinine (serum creatinine > 1.2 mg/dl was taken as a reflection of impaired renal function).

Fasting lipid profile, virology screen (HBsAg, anti HCV Ab) repeated at least twice separated by three months interval, anti-nuclear Ab, Anti Ds DNA (as a screening tests for SLE), C3 and C4 complements.

Patients were followed up by physical examination and repeated urine examination with 24h urine collection for protein, if necessary, every two to three months, and all data were recorded in their follow up files. Patient's response to treatment was graded as complete when their 24 hour urinary protein fell below one gram, partial when their 24 hour urinary protein fell between one to two gram (National Kidney Foundation/ KDOQI clinical practice guidelines). Blood pressure > 140/90 reflects elevated Blood pressure, whereas DBP > 110 reflects severe hypertension. (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure/ JNC7 Report).

Renal biopsy assessments were based on light microscopy only, using the following stains: hematoxylin and eosin (H&E), periodic acid -Schiff (PAS), Masson's trichrome stain and periodic acid methenamine silver (PAMS) stains were used routinely. Electron microscopy and Immunofluoresence were not available at the time of the study.

Histological criteria for the diagnosis of MPGN were the presence of mesangial hypercellularity , inflammatory cell infiltration, increased mesangial matrix, accentuated lobulation and thickened glomerular capillary basement membrane with tram tract or 'double contour' patterns. The presence of interstitial infiltrate and fibrosis were graded also as mild, moderate, and severe. (ISN /RPC-International Society of Nephrology/ Renal Pathology Society).

Patients positive for HBs Ag were referred for further confirmatory tests: HBeAg, anti HBe Ab, anti HBc Ab (IgG and IgM). Those patients were referred to the Center of Gastrointestinal& Liver disease for interferon therapy and additional follow up of their liver disease.

Statistical analysis

The data was entered and analyzed entirely using computer software program of the Statistical Package for the Social Science (SPSS) version 15.0. Standard approaches were used including frequencies, descriptive summaries, Chi-square test (X^2) with 95% confidence interval and Kolmogorov - Smirnov Z test to obtain the significant differences in the study variables. A P- value of < 0.05 has been considered to indicate the level of significance throughout the study.

Results

Thirty three adult patients with MPGN were taken in this study, 19(58%) males and 14 (42%) females. Their age ranged between 18 and 58 year (mean age 32.3 year) Twenty eight (85%) patients were hypertensive on presentation and 10 (15%) presented with DBP equal or more than 110 mmHg ($P < 0.001$) (Figure-1).

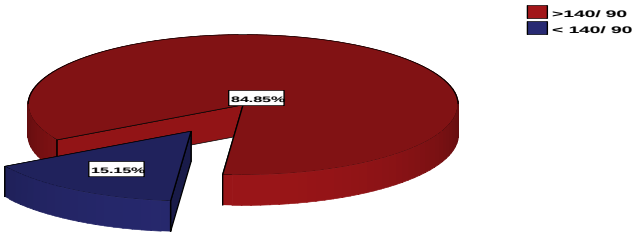


Figure (1): Distribution of patients according to their presentation with elevated blood pressure.

Twenty six (78.7%) patients were found in this study to have primary MPGN and seven Patients (21.2%) with secondary MPGN. Of the secondary MPGN patients, two (6.06%) Patients have been found to have SLE, four (12.1%) patients were positive for HBV Serology, and one (3.03%) patient was positive for HCV. Statistical analysis showed significant differences (P=0.000). (Figure-2).

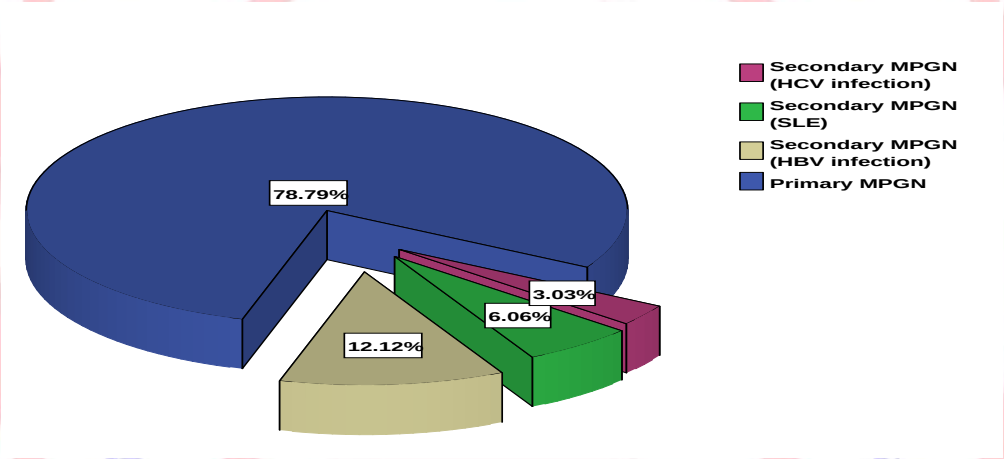


Figure (2): Causes of secondary MPGN.

Patients with positive HBV serology, all those patients were positive for HBs Ag (HB surface Ag), three were positive for HBe Ag (HB envelop Ag) and anti HBc IgM (HB core IgM). The other patient had positive anti HBe Ab.

According to urine examination, proteinurias were found in all patients (100%), hematuria with or without RBC cast were found in 26 (79%) patients. Statistical analysis showed significant differences ($P < 0.001$).as shown in figure 3.

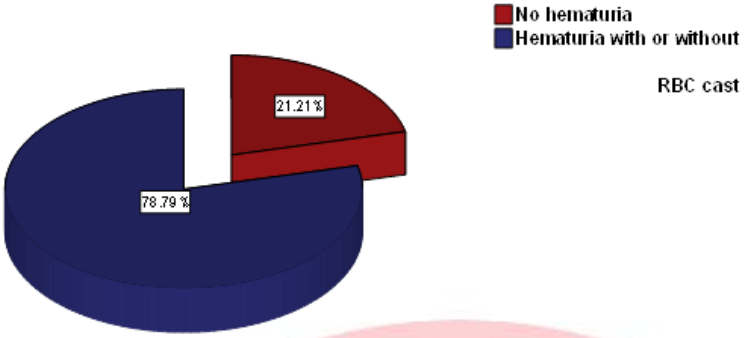


Figure (3): Presentation with hematuria with and without cast.

Twenty four hour urine for protein was more than 3.5 g/24 h/1.73m" in 19 (58%) patients, the others had proteinuria in the range between 0.8 - 2.8 gm/24h statistically significant difference noticed (P < 0.001) as shown in figure (4).

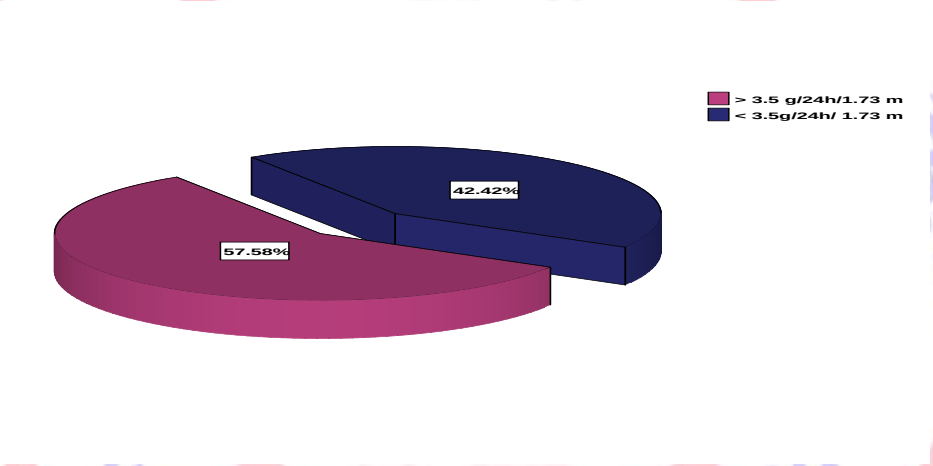


Figure (4): 24h urine protein.

Significant differences (P < 0.001) noticed according to impaired renal function on presentation, serum creatinine >1.2mg/dl, were found in 19 (58%) patients, as shown in figure (5).

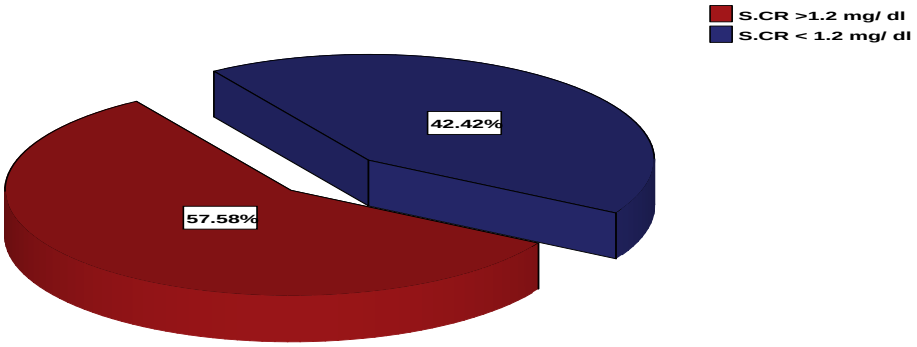


Figure (5): Treatment of patients with primary MPGN and with normal renal function test (s = standard treatment).

According to figure 6 and table 1, Complements (C3and C4) were found to be normal in 15 (45%) patients, for the other 18 (56%) patients, the complements level were low (P=0.042), (P=0.033) respectively.

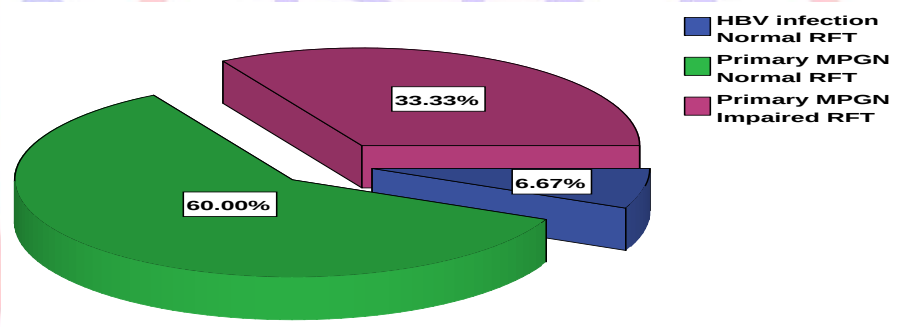


Figure (6): Normal complement level in patients with MPGN.

Table (1): Low complement level in patient with MPGN.

Causes		Low complement level						Total	
		Low C3		Low C4		Low C3 and Low C4			
		No.	%	No.	%	No.	%	No.	%
Primary MPGN		1	8.3	2	16.7	9	75	12	100
Secondary MPGN	HCV	1	100	-	-	-	-	1	100
	SLE	1	50	-	-	1	50	2	100
	HBV	2	66.7	-	-	1	33.3	3	100
Total		5	27.8	2	11.1	11	61.1	18	100

Lipid profile were studied for all the patients and found to have abnormal results as shown in figure 7 (P >0.001).

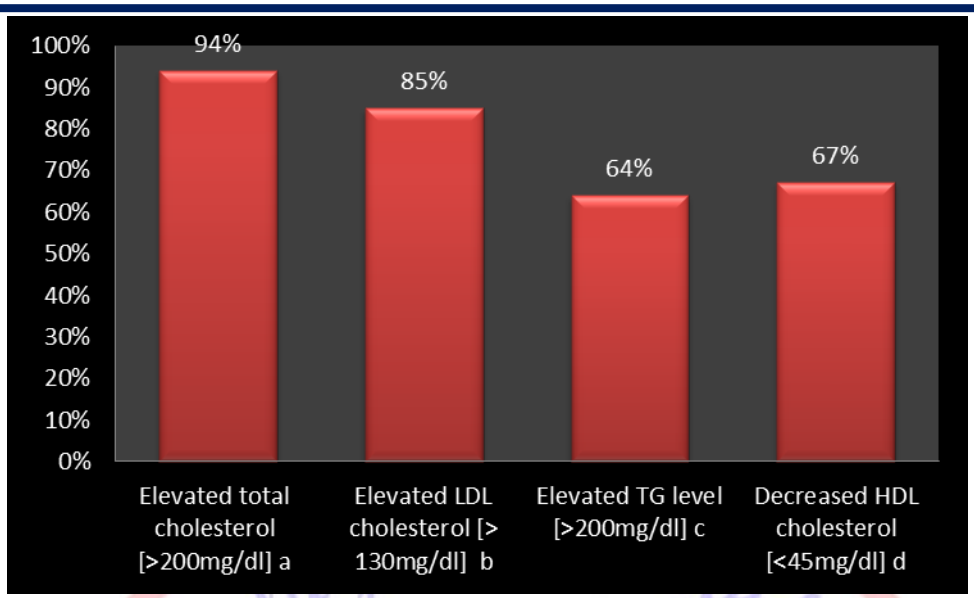
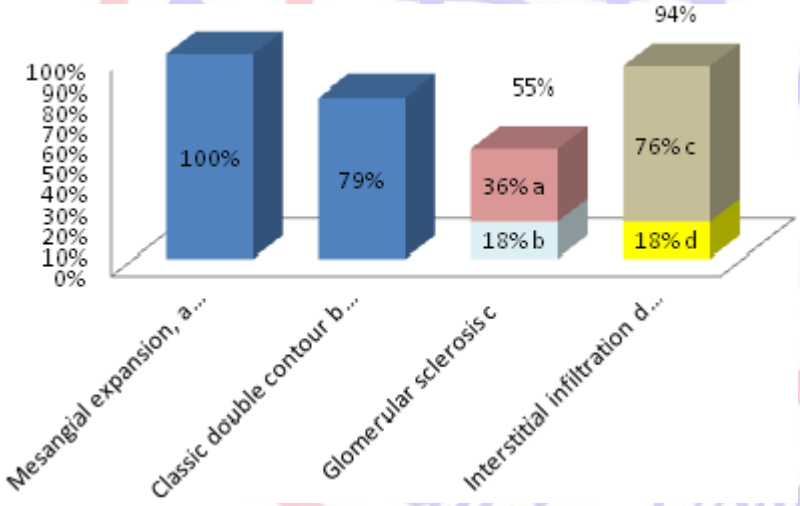


Figure (7): Lipid profile in patient with MPGN.

As shown in figure (8) renal biopsy findings showed prominent hypercellularity, mesangial cells proliferation and mononuclear cells infiltration in all patients. (P >0.001). Electron microscopy was done for three patients (done abroad) and diagnosed type I MPGN.



a: Focal glomerular sclerosis
b: Diffuse glomerular sclerosis
c: Mild to moderate interstitial fibrosis
d: Severe interstitial fibrosis

Figure (8): Renal Biopsy findings in patients with MPGN.

Regarding Course of the disease, patients who presented with normal renal function in the present study were 14(42%), the duration of their illness ranged between 13 to 84 months (mean duration 42.6 months) The renal biopsy in these patients showed no or minimal interstitial fibrosis, 13 patients were negative for hepatitis viruses screen repeatedly, and their collagen disease screen were negative also. One female patient, had repeatedly negative hepatitis virus screen, but after one year of follow up, she developed febrile illness and jaundice and proved to be HBV positive. This patient was maintained on standard treatments only, she had stable renal function test.

The remaining 13 (39%) patients with normal RFT, seven patients were given

steroids; two patients were given MMF, while the remaining four patients were maintained on standard treatment plus dietary protein restriction figure 9.

The standard treatment of all patients was, diuretics, aspirin 100 – 325 mg/day Dipyridamol 375mg/day, statin, ACE I and / or ARB.

The response of those patients to treatment was found to be statistically not Significant (P =0.368).

Steroids were used in seven (21%) patients , prednisolone was given initially in a dose of 1 mg/kg/day(mean dose of 60mg/day) for two to three months then tapered gradually to every other day doses and stopped completely over six months to two years .

Four (13%) patients responded to steroid treatment (two of them completely, other two patients were partial responders). Three (10%) patients did not respond to steroid treatment after six months period. The other six (18%) patients with primary MPGN and normal RFT who did not receive steroid treatment, either because of refusal or because of contraindications to steroids, two patients received mycophenolate mofetil 2g/d for six months and responded by reduction of proteinuria to less than 1g/d. In the remaining four patients, maintained on standard treatment plus dietary protein restriction, two patients only responded with reduction of proteinuria to less than 1g/d, while the other two did not respond Figure (9).

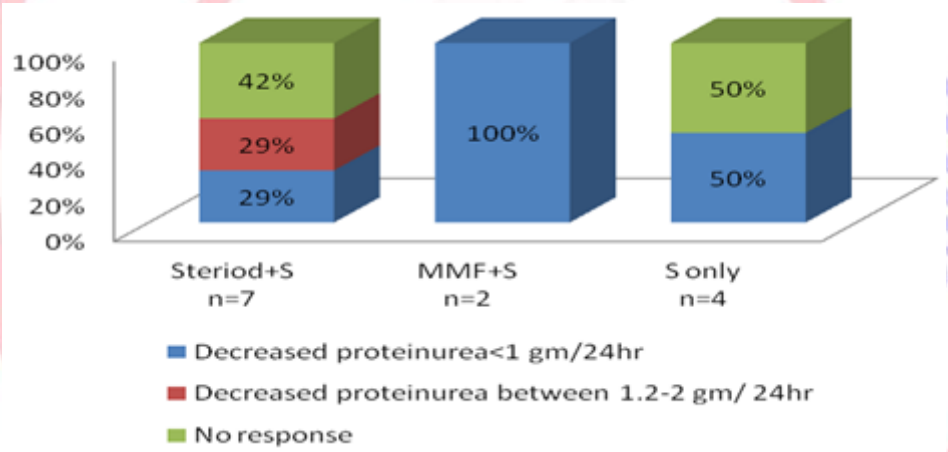


Figure (9): Treatment of patients with primary MPGN and with normal renal function test (s = standard treatment).

The patients who presented with impaired renal function test were nineteen (58%), Thirteen patients with primary MPGN and six patients with secondary MPGN, the duration of their illness ranged between 1.4 months - 10years. Their renal biopsy showed significant glomerulosclerosis (focal or diffuse), interstitial fibrosis, and tubular atrophy. Thirteen (39%) of these patients had negative hepatitis virus screen repeatedly, (six patients were given steroid treatment, four patients, were maintained on standard treatment plus dietary protein restriction, and three patients were given steroid plus MMF).

As shown in figure (10), six (18%) patients were given steroid treatment, only three patients responded by stabilization of renal function test during the follow up period, the other three showed no response and they progressed despite steroid treatment, the other four (12%) patients were given standard treatment without steroid, only one patient showed stabilization of renal function, the other three patients showed progressive deterioration of renal function test. The other

three patients [9%] who were given steroid plus MMF, one patient showed stabilized renal function and proteinuria decreased < 2g/24 h. The other two patients showed progressive decline in RFT. The response of those patients to treatment was found to be statistically not Significant (P = 0.058).

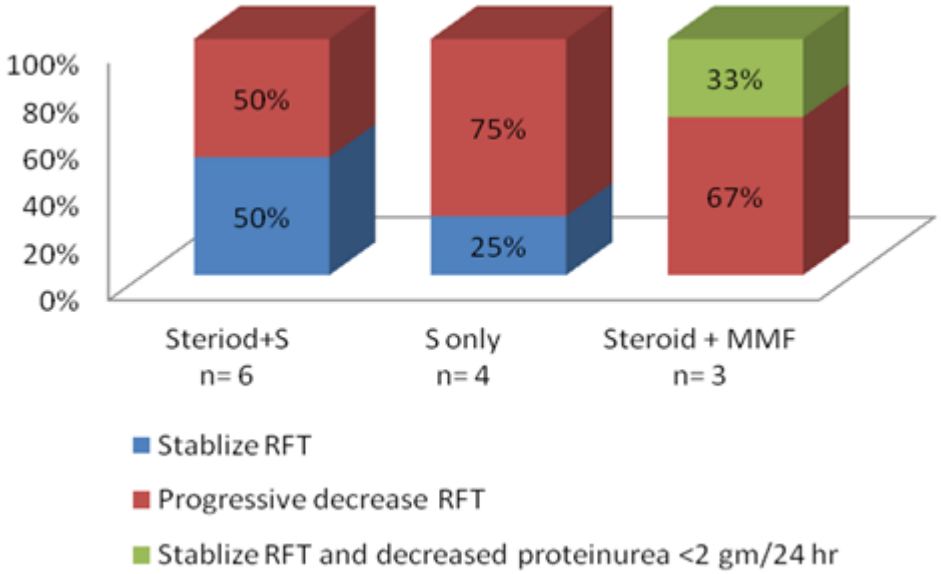


Figure (10): Treatment and results of patients with primary MPGN and with impaired renal function test. (s = standard treatment).

As shown in figure (11), six (18%) patients presented with secondary MPGN and impaired RFT, three patients with positive HBV serology were given antivirus treatment without steroid (two patients were given alpha interferon for one year , the other patient took lamivudine for one year , she refused to take interferon).

Patients who took interferon treatment showed stabilization of renal function test and their proteinuria decreased to less than 1 g /d, while the patient who took lamivudine showed stabilization of renal function but no reduction in proteinuria

One (3.3%) patient was found to have positive HCV serology. This patient showed progressive deterioration in renal function test and became dialysis dependant. He did not receive antivirus treatment.

Two (6.6%) patients with SLE and impaired renal function, their renal biopsy showed class four diffuse proliferative GN, they were given standard treatment plus steroid plus monthly pulses of cyclophosphamide. Their renal function stabilized during the follow up period .One patient was given MMF as maintenance therapy. Statistically significant response to treatment was also not shown in this group of patients statistical analysis not find significant differences (P=0.779).

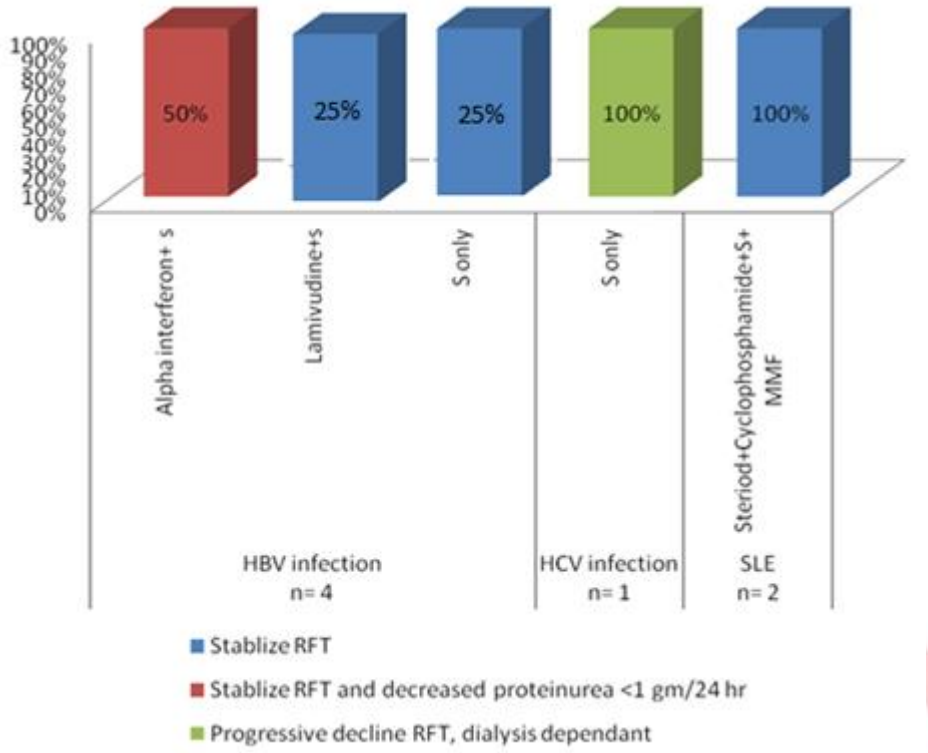


Figure (11): Treatment and results of patients with secondary MPGN.

Discussion

In these study 33 adults patients with MPGN were involved and their different characteristics were described. The cause of MPGN was idiopathic in the majority of cases; it was secondary to HBV and HCV infection and SLE in a minority of cases. Defining idiopathic MPGM in this study is difficult because of the need for an additional laboratory tests that exclude viral illnesses and collagen diseases; in addition many patients were unwilling to repeat the tests or to do more expensive tests because of socioeconomic factors.

Idiopathic MPGN which was relatively common in 1970s and early1980s, is now a rare finding in adults, it has been suggested that more careful screening by blood banks has led to a decline in HCV infection and subsequently GN [18, 19].

In this study 4 out of 7 patients with normal renal function test have responded at least partially by reduction of their proteinuria. Patients with impaired renal function test who received steroid treatment, 50% have stabilized renal function and the other 50% had progressive decline in renal function. Cameron *et al.*, studied 104 patients with idiopathic MPGN, 69 patients had type I and 35 patients had type II. At follow up period of 2 to 21 year, only seven patients showed clinical remission, where as 38% of patients with type I and 49% of patients with type II either died or required dialysis [20].

During the follow up period, in both types, the presence of sclerosis or crescents in the initial renal biopsy was associated with worse outcome but no other feature was of prognostic value [20].In the present study , the presence of sclerosis was also associated with poor response to treatment.

Schena, and Cameron, reviewed a worldwide medical literature about the management of GN in adults and they concluded that therapy has no beneficial effect in patients with MPGN and nephrologists need new drugs that interfere

more decisively with the immune process in those patients [21].

Braun, *et al* (1999), compared the response to treatment and progression of disease in 21 patients with type I MPGN and 25 patients with type II MPGN, with a follow up period of at least five years, and concluded that alternating steroid treatment reduced proteinuria and disease progression in type I but not in type III patients [23].

There is probably better evidence in adults that the rate of progression of MPGN can be slowed by antiplatelet agents [24]. Donadio, *et al* concluded that the combination of aspirin 975 mg/day and Dipyridamol 225mg/day for one year reduces the rate of decline in glomerular filtration rate and reduces the incidence of progression to end stage renal disease [24].

Despite this short term benefit, there was no difference in outcome at 10 years suggesting that prolonged anti platelet therapy is needed if the apparent benefit is to be sustained.

All patients included in this study were receiving anti platelet treatment for at least in the 2 years follow up and intermittently before that, all with other medications. So it was difficult to conclude the benefit of anti-platelet therapy in our patients. Zauner, *et al* treated 18 adults patients with idiopathic MPGN with anti-hypertensive drugs, dietary protein restriction and either placebo or aspirin 500mg/day and Dipyridamol 75mg/day. After three years of therapy, protein fell from 8.3 to 1.6g/day in the anti-platelet treated group. Whether this was associated with improvement in the long term course of the disease is uncertain, since the plasma creatinine concentration was stable in both groups [25].

Two patients in the present study received mycophenolate mofetil (MMF) 2g/day in addition to standard treatment, both of them responded by decreased their proteinuria less than 1g/day. Also 3 patients received MMF with steroids, one patient showed stabilized RFT with reduced proteinuria while the other 2 patients had progressive decline in RFT.

Jones, *et al* treated 5 adults' patients with idiopathic MPGN with oral steroid and MMF There was significant reduction of proteinuria at six months. There were no significant changes in serum creatinine and GFR over 18 months in the treated group. [26]

Hepatitis B virus infection has been implicated in the pathogenesis of three forms of renal disease MGN, MPGN and PAN. There is limited information on the treatment of HBV associated MPGN. The available recommendation is to treat those patients with antivirus therapy. This recommendation is based upon observational data and uncontrolled interventions [27-28]. In this study, patients with HBV infection who received alfa interferon or lamivudine showed stabilized renal function and decreased proteinuria less than 1 g/day. One patient with HCV infection showed progressive decline in renal function and became dialysis dependant.

Lisker- Melman, *et al* assess the efficacy of alfa interferon in patients with HBV related GN. Serum level of HBV DNA decreased in all patients, urine protein excretion also decreased during treatment and their GFR was stable in four years follow up [27]. Conjeevaram, *et al* treated 15 patients with HBV infection and GN with alfa interferon for one year. Eight patients responded well to treatment, in contrast, the seven non responders continued to have evidence of active renal disease and required dialysis. All eight responders have Membranous GN while four of the seven non responders have MPGN [28].

The high incidence of MPGN in non-industrialized countries could be explained in part by the large number and diversity of infectious diseases in these countries. Thus

detailed clinical history and laboratory evaluation for underlying causes is of great importance. In addition, morphological changes, such as tubuloreticular structures (e.g. lupus nephritis, hepatitis) and morphology of deposits, such as in cryoglobulinemia should be carefully evaluated [29].

In Conclusion the present study demonstrates, although statistically not significant, that patients who presents with normal RFT have better response to treatment than patients who presents with impaired RFT. Their renal biopsy showed minimal interstial fibrosis Also patients with secondary MPGN (HBV and SLE) have responded at least partially to antiviral and / or immunosuppressive therapy. The relatively short follow up (2 years) and the unavailability of IF and EM have made an important limitation to the study. Thus the availability of such resources plus complements study is needed to diagnose the diverse morphologic patterns of MPGN. Given immunosuppressive treatment for adults with MPGN (steroids, and cytotoxics) needs careful selection because of the high incidence of undiagnosed secondary causes of MPGN.

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