Treatment Aspects of Primary Nephrotic Syndrome in Adults

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Abstract

Strict therapy protocol, which would be used universally for certain morphological forms of primary nephrotic syndrome, does not exist. The aim of the study was to show the effects of used therapy protocol in treatment of primary nephrotic syndrome at the Institute of Nephrology, Clinical Center University of Sarajevo in period of 2000-2005. The retrospective analysis covered 48 patients (17 women and 31 men) with idiopathic nephrotic syndrome, where pathomorphological changes were proved by kidney biopsy. Minimal change disease was confirmed with 6 (12,5%) patients. All patients were initially treated with corticosteroids with dose of 1mg/kg of body weight. Five patients were in the group of primary responders (83,3%) with long term total remission, and 1 patient (16,6%) was a primary responder with 3 relapses in 8 months with a therapy of corticosteroids and bolus of cyclophosphamide. Diffuse mesangial proliferative glomerulonephritis was shown in 13 patients (27,1%). Seven patients from this group were treated with corticosteroid therapy (1 mg/kg of body weight for 4 weeks, followed by 0,5 mg/ kg of body weight until therapeutical response was achieved, and finally gradual exclusion of therapy after eight weeks in responsive patients). Six patients were treated with corticosteroids and one-month of bolus cyclophosphamide during half of year (10 -15 mg/kg of body weight). Total remission was achieved in 37,9% of the patients. The IgA nephropathy presented with the nephrotic syndrome was shown in 10,4% (5) of the patients. Three patients from this group were treated with corticosteroid therapy (1 mg/kg of body weight for 4 weeks, followed by 0,5 mg/ kg of body weight until therapeutical response was achieved, and finally gradual exclusion of therapy after eight weeks in responsive patients) and 2 patients with corticosteroids and cyclophosphamide (1,5 mg/kg of body weight) during 6 months. Complete remission of nephrotic syndrome from this pathomorphological cathegory was achieved in 2 patients. Membranoproliferative glomerulonephritis was shown in 6 patients (12,5%). All were treated with corticosteroids plus bolus of cyclophosphamide. Partial remission was achieved in one patient. Membranous glomerulonephritis was confirmed in 18 patients (37,5 %). Combined therapy of corticosteroids and bolus of cyclophosphamide was used in 7/18 patients, in 2/18 patients therapy of corticosteroids and per os cyclophosphamide (2 mg/kg of body weight) and in 9/18 patients cyclosporine therapy (3 mg/kg of body weight). Complete remission was achieved in 38,8% of the patients. A high percentage of achieved remissions of primary nephrotic syndrome in adults shows the efficiency of immunomodulating therapy used. Membranoproliferative glomerulonephritis still remains a therapy problem.

KEY WORDS: nephrotic syndrome, glomerulonephritis, treatment, outcome

Introduction

Primary nephrotic syndrome (NS) is a consequence of immunoreactive glomerulopathies of unknown cause and is characterised with massive proteinuria, hypoalbuminaemia, hyperlipidaemia and oedema. It is presented by various histological appearances of glomerular disease. The problem of treatment of glomerular diseases is complex and multifactorial. Thanks to many researchers and analyses, nowadays we have more or less accepted principles of primary nephrotic syndrome treatment (1). However, universal therapeutic protocol, which will be used for every specific morphological form of treatment, doesn't exist. The aim of this paper was to evaluate the effects of applicable therapy protocols in treating patients with primary nephrotic syndrome at the Institute of Nephrology Clinical Centre University (CCU) in Sarajevo in period from 2000 to 2005. The average observation period for each patient was one year.

Subjects and Methods

The retrospective analysis covered 48 patients (17 male and 31 female), treating due to primary nephrotic syndrome at the Institute of Nephrology Clinical Centre University in Sarajevo in period between 2000 - 2005. All patients had pathomorphological changes, proved by renal biopsy, and fulfilled the basic criteria for diagnosing primary NS. Previously, all secondary causes of nephrotic syndrome were excluded through the relevant clinical investigations. Kidney biopsy was performed under ultrasound control by the usage of biopsy gun with 29-cm-long needles of 18G (1,2 mm), during which two cylindrical samples of kidney tissue were taken. Pathohistological analysis included the light and immunofluorescent analyses of kidney tissue. The outcome of the used treatment was followed by monitoring the level of total serum proteins, proteinuria and creatinine clearance. Analysis results obtained before the treatment were used as basic data, while those obtained after a year of treatment and monitoring were used as comparative data for making the assessment on treatment outcome achieved. The outcome of the disease was defined as:

1) Complete remission of NS – proteinuria less then 0,25 g/day in three consecutive measurings
2) Partial remission of NS – proteinuria between 0,25 g/day and 3,5 g/day in three consecutive measurings
3) Persistence of NS – proteinuria more than 3,5 g/day in three consecutive measurings

The test results were statistically processes using descriptive statistics and Student-t test for the evaluation of statistical significance of differences among mean values of monitored parameters along with the acceptance of statistical significance at the level $p<0,05$. The results are shown in graphic and tabular form.

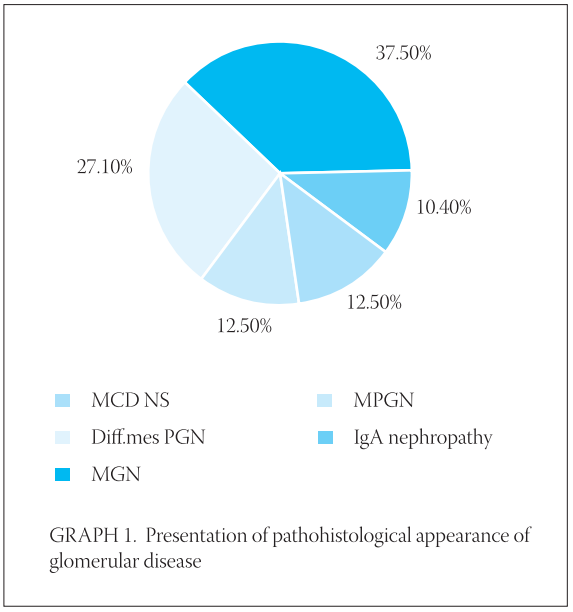
Results

CATEGORIZATION OF HYSTOLOGICAL CHANGES

Graph 1 shows the frequency of pathohistological types of glomerulonephritis. Membranous glomerulonephritis (MGN) is the most common cause of primary nephrotic syndrome (37,5%), and than followed-up by diffuse mesangial proliferative glomerulonephritis (27,1%, diff.mesPGN). Minimal change disease (MCD) presents pathohistological base in 12,5% of the patients with primary nephrotic syndrome (NS), as well as membranoproliferative glomerulonephritis (MPGN), while IgA nephropathy is presented in the lowest number of the patients with primary nephrotic syndrome (10,4%).

AGE OF PATIENTS WITH PRIMARY NEPHROTIC SYNDROME

Most of the patients with primary NS were at the age of 41-60 years (37,21%), with approximative equal appearing in the groups younger than 20 and older than 60 years (13,95% vs 16,28%). It is interesting that 50% of patients with MCD were above 60 years old. Primary NS appeared more frequently in male than in female (70,8% male vs. 29,2% female). Table 1 shows the mean age of the patients with primary nephrotic syndrome in relation to pathomorphology catagories of glomerular diseases.



GRAPH 1. Presentation of pathohistological appearance of glomerular disease

SPECTRUM OF PRIMARY NEPHROTIC SYNDROME TREATMENT

Table 2. shows the mode of the treatment and number of the patients according to pathohistological categories. Corticosteroids (initial dosage 1-1,5 mg/kg BW/4 weeks, then dosage reduction to 0,5 mg/kg BW until the achievement of therapeutic response, followed by gradual termination of therapy 8 weeks after achieved the therapeutic response) were the basis of therapy protocol for patients with diffuse mesangial proliferative glomerulonephritis, IgA nephropathy and minimal change disease NS. The patients with diffuse mesangial proliferative glomerulonephritis, resistant to corticosteroids only, as well as corticosteroid resistant MCD NS, were treated with the combination of corticosteroids and pulse therapy of cyclophosphamide (10-15 mg/kg BW), or with cyclosporine (3 mg/kg BW, level of cyclosporine in blood app. 100 ng/ml). The patients with membranous glomerulonephritis (MGN) were the most frequently treated with cyclosporine (3 mg/kg BW), or with the combination of corticosteroid and pulse therapy of cyclophosphamide. Therapy protocol with pulse doses of cyclophosphamide and corticosteroids was applied also in the treatment of patients with membranoproliferative glomerulonephritis (MPGN). Table 3. shows the treatment results of the patients with primary nephrotic sindrome. In the patients with MCD, complete remission of nephrotic syndrome was achieved in 100% of the cases, by using corticosteroids as the first line of treatment. In one patient, primary responder - frequent relapser, after achieved remission of the disease by initial therapy with corticosteroids, one-month bolus of cyclophosphamide was added to the corticosteroids therapy due to 3 relapses in 8 months, which resulted in complete remission NS after the second one-month bolus of cyclophosphamide. In patients with diffuse mesangial proliferative glomerulonephritis complete remission was achieved in 37,9% (5) of the cases. Only corticosteroids were used with 3 patients, while pulse therapy of cyclophosphamide with corticosteroids was used with 2 patients. Partial remission of NS was achieved in 26,3% of the cases. The remaining 35,8% of the patients also treated, still showed the signs of persistent nephrotic syndrome. Complete remission of nephrotic syndrome was achieved in 40% of the patients with IgA nephropathy, while the remaining 60% treated patients showed the signs of partial remission. In treated patients with membranous glomerulonephritis, complete remission was achieved in 7 (38,8%) patients. Six of them (71%) were treated only with cyclosporine, and one patient was treated with combination of corticosteroids and cyclophosphamide. Partial remission was achieved in remaining 11 (61,2%) patients. The patients with membranoproliferative glomerulonephritis (MPGN) didn't have positive reaction on treatment with corticosteroids and associating bolus therapy of cyclophosphamide (table 5). The signs of nephrotic syndrome persisted in five treated patients during the follow-up period,

PATHOHISTOLOGIC FORM OF NS	MINIMAL CHANGE NS	DIFFUSE MESPGN	IGA NEPHROPATHY	MGN	MPGN
years old	49,66±18,67	34,89±15,09	28,5±5,4	46,56±9,71	38,0±9,05

TABLE 1. Age of patients with primary nephrotic syndrome

PATOHISTO-LOGICAL CHANGE	TYPE OF TREATMENT WITH NUMBER OF TREATED PATIENTS			
	Corticosteroids + bolus cyclophosphamide	Cyclosporine	Corticosteroids	Cyclophosph. per os + corticosteroids
Diff.mesPGN	6	-	7	-
IgA nephropathy	-	-	3	2
MGN	7	9	-	2
MCD	1	-	5	-
MPGN	6	-	-	-

TABLE 2. Treatment of primary nephrotic syndrome

OUTCOME	MCD NS	Diff.mesPGN	IgA nephropathy	MGN	MPGN
Complete remission	100%	37,9%	40%	38,8%	-
Partial remission	-	26,3%	60%	61,2%	16,7%
Persistent NS	-	35,8%	-	-	83,3%

TABLE 3. Outcome primary nephrotic syndrome treatment

PROTEINURIA	MCD NS	Diff.mesPGN	IgA nephropathy	MGN	MPGN
Complete remission	6,5±1,76 vs. 0,54±0,38 p<0,001	4,93±2,49 vs. 0,24±0,12 p<0,001	4,56±2,3 vs. 0,23±0,05 P<0,001	8,52±4,27 vs. 0,21±0,05 p<0,001	-
Partial remission	-	5,44±2,89 vs. 2,09±0,74 p<0,05	5,81±1,3 vs. 2,96±0,6 p<0,05	8,06±1,21 vs. 2,52±0,52 p<0,001	4,81±1,3 vs. 1,96±0,6 p<0,05
Persistent NS	-	6,2±2,0 vs. 7,4±2,93p=0,58	-	-	12,06±4,2 vs. 9,5±3,8 p=0,67

TABLE 4. Therapy effects on proteinuria

PATHOHISTOLOGICAL CATEGORY	CREATININE CLEARANCE (ML/MIN)	
	BEFORE THE THERAPY	AFTER THE THERAPY
MCD (X±δ)	109,66±8,26	96,33±20,15
p values	0,164	
Diff.mesPG(X±δ)	130,16±45,16	113,88±22,26
p values	0,597	
IgA nephropathy	105,05±10,2	99,88±8,5
p values	0,553	
MGN (X±δ)	98,07±38,25	88,74±19,13
p values	0,574	
MPGN (X±δ)	38,3±9,5	34,45±5,2
p values	0,256	

TABLE 5. Therapy effects on creatinin clearance

while partial remission was achieved in only one patient. Table 4 shows the treatment results of the patients with nephrotic syndrome in relation to quantitative values of proteinuria as a parameter of the disease activity and for assessment of disease degree control. The therapy protocols applied in all pathohistological forms of primary nephrotic syndrome were not followed by the deterioration of kidney function. Creatinin clearance did not change significantly in the period monitored.(Table 5).

Discussion

Glomerular diseases, responsible for primary nephrotic syndrome, show different histological appearances. In 12,5% of our patients with primary nephritic syndrome, pathohistological changes belonged to minimal change disease. In 5 patients, MCD was treated with corticosteroids, while in one case pulse therapy of cyclophosphamide was added to corticosteroids due to relapsing NS. All treated patients (100%) achieved complete remission for two months of the treatment. Although MCD is the most frequent form of idiopatic nephrotic syndrome in children and adolescents (2), with 90-95% patients-responders on steroid therapy (3), a large clinical trials on adult patients with MCD nephrotic syndrome also showed by corticosteroids induced remission of nephrotic syndrome in 81-95% of the treated cases (4,5). Our patients with MCD NS, although a high average age, also showed a significant steroid sensitivity. Diffuse mesangial proliferative glomerulonephritis was proved in 27,1% of the patients with primary nephrotic syndrome, with more frequent occurence in men (70,8%) than in women (29,2%). According to some authors, this type of glomerular disease in adults is presented by nephrotic syndrome in 15-35% of the cases (6). Alexopoulos and colleagues (7) achieved complete remission with corticosteroids therapy in 36% of treated patients with diffuse mesangial proliferative glomerulonephritis. We achieved complete remission of nephrotic syndrome in about 1/3 of treated patients (37,9%). IgA nephropathy is the most common form of glomerular lesion, but it is rarely present with signs of primary nephrotic syndrome (8). In our patients with nephrotic syndrome this type of glomerulonephritis is also the most rarely form of glomerular lesion. Most of the patients with IgA nephropathy are younger than 30 years, with histological changes belonging to subclass IV. Complete remission was achieved in 2/5 of the patients with cordicosteroid therapy, and in three patients with corticosteroids in combination with cyclophospha-

mide per os. While some authors recommend the use of high doses of corticosteroids as treatment strategy of IgA nephropathy (9), others recommend the combination of pulse doses of methylprednisolone and cyclophosphamide i.v. every month, during six months (10). Membranous glomerulonephritis is the most common cause of primary nephrotic syndrome in adults (11), which is confirmed by our results (37,5%). Complete remission of nephrotic syndrome was achieved in 7/18 (38,8%) of treated patients, and most of the responders (71%) developed complete remission only by cyclosporine. Partial remission was achieved in remaining 61,2% of the patients. During the treatment, in all patients with membranous glomerulopathy, kidney function has been preserved. Some authors noticed the efficacy of cytotoxic agents, like cyclophosphamide and clorambucile, and also promising effects of cyclosporine (12). Membranoproliferative glomerulonephritis was proved in six patients with primary nephrotic syndrome. Steroid therapy in combination with pulse doses of cyclophosphamide resulted in partial remission in only one from six of our patients. All patients with this pathohistological lesion showed the renal function reduction in time of the making disease diagnosis. Heavy proteinuria, microhaematuria and renal failure with present high blood preassure suggested the worse outcome in this kind of glomerular disease.

Conclusion

- The greatest number of patients with primary nephrotic syndrome analysed had the histological appearance of membranous glomerulonephritis.
- All patients with minimal change NS achieved complete remission of NS.
- Corticosteroids were the first line chosen drugs in minimal change NS treatment in adults.
- The use of corticosteroids with the pulse doses of cyclophosphamide resulted in satisfactory therapeutic answer in diffuse mesangial proliferative glomerulonephritis treatment.
- Membranous glomerulonephritis had the best therapeutic answer on cyclosporine therapy.
- Membranoproliferative glomerulonephritis still remains a therapy problem.

References

(1) Cappo R., Amore A. New perspectives in treatment of glomerulonephritis. Pediatr. Nephrol. 2004; 19:256-265.

(2) De Carvalho Panzeri Carlotti A.P., Franco P.B., Elias L.L., Facincani I., Costa E.L.C., Foss N., Moreira A.C., de Casto M. Glucocorticoid receptros, in vitro steroid sensitivity, and cytocine secretion in idiopathic nephrotic syndrome. Kidney Int. 2004; 65:403-408.

(3) Hadson E.M., Knight J.F., Willis N.S., Craig J.C. Corticosteroid therapy in nephrotic syndrome: a meta-analysis of randomised controlled trials. Arch. Dis. Child. 2000; 83:45-51.

(4) Nolasco F., Cameron J.S., Heywood E.F., Hicks J., Ogg C., Williams D.G. Adult-onset minimal change nephrotic syndrome: a long-term follow-up. Kidney Int. 1986; 29:1215-1223.

(5) Tune B.M., Mendosa S.A. Treatment of the idiopathic nephrotic syndrome. J. Am. Soc. Nephrologists 1997; 8(5):769.

(6) Galla J.H. IgA nephropathy. Kidney Int. 1995; 47:377-387.

(7) Alexopoulos E., Papagianni A., Stangou M., Pantzaki A., Papadimitrou M. Adult-onset idiopathic nephrotic syndrome associated with pure diffuse mesangial hypercellularity.Nephrol. Dial. Transplant. 2000; 15: 981-987.

(8) Feehally J. Aspects of IgA nephropathy. BANTAO Journal 2005; 3(2):78.

(9) Katafuchi R., Ikeda K., Mizamasa T., Tanaka H., Ando T., Yanase T., Masutan K., Kubo M., Fujimi S. Controlled, prospective trial of steroid treatment in IgA nephropathy: a limitation of low-dose prednisolone therapy. Am. J. Kidney Dis. 2003; 41:972-983.

(10) Hruby Z. What is new in therapy of glomerulonephritis in the 2003/2004. Annales Academiae Medicae Bialostocensis 2004; 49:166-169.

(11) Hogan S.L., Muller K.E., Jennette J.C., Falk R.J. A review of therapeutic studies of idiopathic membranous glomerulopathy. Am. J. Kidney Dis. 2004; 44(3):862-875.

(12) Cattran D.C., Appel G.B., Hebert L.A., Hunisicker L.G., Pohl M.A., Hoy W.E., Maxwell D.R., Kunis C.L. Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial. Kidney Int. 2001; 59:1484-1490.