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The Functional Outcome of Normal or High Blood Pressure in Patients with Chronic Glomerulonephritis and Nephrotic Syndrome is Dependent on Association with Functional, Histologic and, Proteinuric Parameters

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Abstract

Background: Normal (BP0) or high Blood Pressure (BP1) are variably present in patients with chronic Glomerulonephritis (GN) and Nephrotic Syndrome (NS). At biopsy each BP0 or BP1 patient is associated with different values of renal function, urinary proteins excretion and renal lesions severity [GGS%, TID and AH score]. Thus, outcome of BP0 and BP1 may be dependent in every patient by the associations with these parameters and by eventual treatments with immunosuppressive agents.

Methods: In 151 patients with GN and NS the outcome was evaluated in BP0 and BP1 patients according to eGFR≥ or <60 ml/min/1.73 m^2. In 140 patients with renal biopsy performed at the same time of all parameters the outcome was evaluated for 3 types of renal lesions severity (GGS%, TID score and AH score) and according to 4 groups of combined urinary excretion of IgG/C and α2m/C. The treatment with steroids and cyclophosphamide was evaluated. Aim of study: Identify which functional, Proteinuric. Histologic and therapeutic factors in combination with BP0 and BP1 are associated with outcome improvement or worsening.

Results: In BP 0 patients the highest rate of "Remission & persistent NRF ("No progr") is 100% observed in BP0 patients associated with IgG/C&α2m/C group 0+0 and treated with Steroids and Cyclophosphamide.

The percentages of "noprogr" of the other parameters were: TID score 0 (96%), AH score 0 (87.5%), eGFR ≥ 60 ml/min (84%). In BP 1 the worse rate of "Progression & progression risk" ("progr") is 100% observed in BP1 patients associated with IgG/C&α2m/C group 1+1 and treated with Steroids and Cyclophosphamide; the "progr" percentages of the other parameters were: TID score 4-6 (96%), AH score 2-3 (96%), IgG/C & α2m/C group 1+1 (85%), eGFR < 60 ml/min (82%).

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Conclusions: The outcome in BP0 and BP1 patients is dependent on their association with some parameters: renal function, renal lesions severity and some Proteinuric parameters alone or in combination.

Introduction

The clinical significance of arterial hypertension in renal diseases has been evaluated in several studies [1-12]. In a cohort of 151 patients with chronic Glomerulonephritis (GN) and Nephrotic Syndrome (NS) normal (BP 0) and high Blood Pressure (BP 1) are present with variable percentage according to several factors: eGFR ≥ or < 60 ml /min73.1 m^2; GGS: 0% *vs.* ≥ 20%; TID score 0 *vs.* 4-6; AH score 0 *vs.* 2-3, TUP/C < *vs.* ≥ median and combined excretion of IgG/C and α2m/C groups (for these groups definition see later in Laboratory analysis Section). The combination of each patient with one or more functional, histologic and Proteinuric parameters and eventual treatment with Steroids and Cyclophosphamide is associated with different percentages of favourable outcome (Remission and PNS with long lasting NRF": briefly defined "noprogr.") or unfavourable outcome (ESRD & eGFR < 50% of baseline & PNS with CRF: briefly defined "progr"). Aim of the study: assess how high blood pressure increases according to lower values of eGFR and increased values of the main histological parameters such as Global Glomerular Sclerosis (GGS%), extent of Tubulo-Interstitial Damage (TID score) and Arteriolar Hyalinosis (AH score) and how functional outcome may improve or worse according with the association with these functional, Proteinuric and histologic parameters.

Patients and methods

The patients cohort included in the study was not selected. The patients attending the Nephrology and Dialysis Unit of San Carlo Borromeo Hospital, Milan, Italy, between January 1992 and April 2006 with renal biopsy diagnosis of GN with NS were 204; 26 patients with Acute Reversible Renal Failure (ARF) at biopsy were excluded from analysis as do not meet the inclusion criterion (chronic glomerulonephritis). The 151 have functional outcome and 84 of them were selected for treatment with Steroids and Cyclophosphamide. The diagnosis of all 151 patients were: Crescentic IgAN (CIgAN) n. 12, Focal Segmental Glomerulosclerosis (FSGS, n. 32), IgAN (2), Idiopathic Membranous Nephropathy (IMN, n. 66), Minimal change disease (MCD, n. 11), Membrano-Proliferative Glomerulonephritis (MPGN, n. 15): Lupus Nephritis [LN, n. 13: (WHO LN classes: 4: n. 11; 5 n. 2)]. Inclusion criteria: nephrotic syndrome (proteinuria ≥3.5 g/24 h and/or serum albumin <3.0 g/dL); at least six glomeruli in renal biopsy; typical features at light and immunofluorescence microscopy; no clinical signs of secondary GN except for LN. The functional outcome was evaluated in all 151 patients with rather long follow up [mean 91±77 months, 2-311]. Five types of outcome were considered: 1) Remission of NS: complete: proteinuria ≤ 0.30 g/24 h; partial: proteinuria ≤ 2.0 g/24 h; 2) persistent NS with long lasting normal renal function (PNS NRF) after a follow up of 91±73 months (30-200); 3) Progression To End-Stage Renal Disease (ESRD); 4) eGFR reduction ≤ 50% of baseline; 5) persistent NS with Chronic Renal Failure (CRF) and progressive eGFR reduction (from 49.3 to 39.1 ml/min/1,72 m^2). Usually in prediction studies, the outcomes considered are Remission and ESRD. We decided to evaluate not only each type of outcome considered alone but the combination of outcomes with similar prognostic significance: thus Remission was evaluated in combination with persistent PNS with long lasting NRF, afterwards indicated as ""noprog."; ESRD and eGFR ≤ 50% were evaluated in combination with persistent PNS with CRF characterized by eGFR reduction from 49.3 to 39.1 ml/min/1.72 m^2 and thus candidate for progression to ESRD, afterwards indicated as "progr".

Laboratory analysis

Proteinuria was measured in 24-hour urine collection and second morning urine sample by the Coomassie blue method (modified with sodium-dodecyl-sulphate) and expressed as 24/hour proteinuria and protein creatinine/ratio (mg urinary protein/g urinary creatinine). Serum αand urinary creatinine were measured enzymatically and expressed in mg/dL. Serum albumin and IgG and urinary IgG, α2-macroglobulin (α2m), Albumin and α1-microglobulin (α1m) were measured by immunonephelometry; urinary proteins were expressed as urinary protein/creatinine ratio (IgG/C, α2m/C, Alb/C, α1m/C). Estimated glomerular filtration rate (eGFR) was measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [13]. Three types of renal lesions that are markers of disease severity in any type of GN were evaluated: percentage of glomeruli with Global Glomerulosclerosis (GGS%); extent of Tubulo-Interstitial Damage (TID) evaluated semi-quantitatively by a score: tubular atrophy, interstitial fibrosis and inflammatory cell infiltration graded 0, 1 or 2 if absent, focal or diffuse (TID global score: 0-6); extent of Arteriolar Hyalinosis (AH) evaluated semiquantitatively by a score: 0, 1, 2, 3 if absent, focal, diffuse, diffuse with lumen reduction, respectively (AH global score 0-4). In our recent study [14] in 151 patients with GN and NS, were calculated the median of IgG/C (IgG/C 0<median and IgG/C >median); the median of α2m/C was calculated independently in IgG/C 1 and IgG/C 0 patients, respectively and defined α2m/C 0 and α2m/C 1 if < or > the median. On the basis of combination of IgG/C and α2m/C medians were defined 4 groups: IgG/C 1 & α2m/C 1, IgG/C 1 & α2m/C 0, IgG/C 0 & α2m/C 1, IgG/C 0 & α2m/C 0) more briefly defined (1+1, 1+0, 0+1, 0+0). These groups assess disease severity of all patients: moreover, the combination of BP 1 with (1+1) group and BP 0 in combination with (0+0) group predict 100% of "progr" and 100% of "noprogr" respectively (Table 1).

Table 1: Functional outcome in 84 patients treated with Steroids and Cyclophosphamide according to the 4 groups of combined IgG/C & α2m/C excretion (1+1, 1+0, 0+1, 0+0) in combination with BP 1 and BP 0.

	IgG/C1&α2m/C1 & BP 1 n. 14	IgG/C1&α2m/C1 n. 7	IgG/C 1&α2m/C 0 n. 21	IgG/C 0&α2m/C 1 n. 21	IgG/C 0&α2m/C 0 n. 6	IgG/C 0& α2m/C 0 & BP 0 n. 15	IgG/C 1&α2m/C 1 vs IgG/C 0&α2m/C 0 p
Age yrs.	46 ± 20	42 ± 18	37 ± 18	38 ± 16	41 ± 19	37 ± 18	0.83
eGFR baseline	31.2 ± 19.1	46.0 ± 29.9	74.1 ± 27.4	67.1 ± 26.6	97.9 ± 25.3	105.9 ± 22.4	<0.0001
Follow up months	66 ± 72	68 ± 70	96 ± 79	85 ± 85	117 ± 76	114 ± 67	0.03
TUP/C	5933 ± 2125	5795 ± 2043	7373 ± 4406	3781 ± 2223	3194 ± 2423	3543 ± 2683	0.0005

IgG/C	448 ± 196	434 ± 181	101 ± 148	112 ± 41	63 ± 32	53 ± 31	<0.0001
α2m/C	24.97 ± 13.3	26.64 ± 23.0	6.00 ± 4.34	6.76 ± 7.65	0.12 ± 0.54	0 ± 0	<0.0001
Alb/C	4823 ± 1645	4639 ± 1676	3376 ± 5982	3310 ± 1975	3258 ± 2592	3408 ± 2881	0.02
α1m/C	91.6 ± 37.3	79.4 ± 45.3	56.2 ± 29.3	37.9 ± 20.8	18.8 ± 10.4	19.2 ± 10.8	<0.0001
GGS 0%		2			11		
TID score 0		0			10		
AH score 0		3			17		
BP 1	100%	14 (67%)			6 29%)	0%	
Rem. PNS NRF "noprogr"	0 (0%)	(19%)	(48%)	(62%)	34 (89%)	(100%)	
ESRD+PNSCRF+ eGFR ≤ 50% "Progr"	14 (100%)	(81%)	(52%)	(38%)	1 (4%)	0%	

Table 2: Baseline clinical, functional, Proteinuric and histologic parameters in 151 patients with glomerulonephritis (GN) and Nephrotic Syndrome (NS) (CIgAN n.12, FSGS n. 32, MCD n. 11, IgAN n. 2, IMN n.66, MPGN n.15, LN n.13) 61 with baseline normal Blood Pressure (BP 0) and 90 with high Blood Pressure (BP 1).

	Normal BP (BP 0) n. 61 (40%) <140/90 mmHg	High BP (BP 1) n. 90 (60%) ≥ 140/90 mmHG	P
Age yrs.	38.4 ± 16.5	43.6±18.1	
eGFR baseline	94.3 ± 22.4	57.1 ± 28.9	<0.0001
eGFR last	75.2 ±33.4	39.8± 32.5	<0.0001
eGFR basel. ≥ 60	n. 57	n. 40	
eGFR basel. < 60	n. 4	n. 50	
TUP/C	4086 ± 2731	5018 ± 3375	0.06
IgG/C	142 ± 140	296 ± 335	0.0001
α2m/C	6.64 ± 16.50	11.64 ± 16.76	0.07
Alb/C	3469 ± 2397	4089 ± 2563	0.13
α1m/C	28.9 ± 26.8	59.4 ± 47.6	<0.0001
GGS%	4.7 ± 8.2	17.0 ± 17.7	<0.0001
TID score	1.01 ± 1.18	2.48 ± 1.76	<0.0001
AH score	0.19 ± 0.44	0.76 ± 0.85	< 0.0001
IgG/C & α2mC 0+0	26 (43%)	12 (13%)	
IgG/C & α2m/C 0+1	12 (20%)	25 (28%)	
IgG/C & α2m/C 1+0	11 (18%)	27 (30%)	
IgG/C & α2m/C 1+1	12 (20%)	26 (29%)	

Statistical analysis

Continuous variables are expressed as means±SD. Categorical variables are expressed as the number of patients (%). The differences of mean were determined by t-test; categorical variables by the chi-square test. All statistical analyses were performed using Stata 15.1 (StataCorp LP, TX, USA). Two-sided p<0.05 was considered statistically significant.

Results

The functional outcome has been evaluated according to the highest and lowest values of eGFR (≥ *vs.* < 60 ml/min), GGS 0% *vs.* ≥ 20%, TID score 0 *vs.* 4-6 and AH score 0 *vs.* 2-3. The outcome was classified as "noprog" (remission and persistent NS with long lasting normal renal function) and "progr" (ESRD, eGFR < 50% of baseline and persistent NS with CRF). In general the patients with more severity of renal function and histological parameters show an increase of percentage of patients with high blood pressure, while the patients with eGFR ≥ 60 ml/min, GGS 0%, TID score 0 and AH score 0 usually show an increase of patients with normal blood pressure. The functional outcome was also evaluated according to groups of combined urinary excretion of IgG/C & α2m/C (0+0, 0+1, 1+0, 1+1).

Outcome in BP 0 and BP 1 patients according to level of renal function eGFR ≥ or < 60 ml/min

In all the 151 patients with GN and NS 61 patients (40%) have normal Blood Pressure (BP 0) and 90 patients (60%) have high Blood Pressure (BP 1); In 61 BP 0 patients "No progr" is 80% and "Progr." 20%; in 90 BP 1 patients "no progr." 42% and "progr." is 58% (Table 2). BP 0 and BP 1 are highly significant different for baseline and last eGFR, IgG/C, α1m/C, GGS%, TID score and AH score (Table 2).

Table 3: Outcome according to eGFR ≥ *vs.* <60 ml/min, GGS 0% *vs.* ≥20%, TID score 0 *vs.* 4-6. AH score 0 *vs.* 2-3 In combination with BP 0 and BP 1.

		Remission &PNS NRF "no progr"	ESRD & eGFR <0% & PNS CRF "Progr"
All pts BP n.151			
All pts	BP 0 n. 61 (40%)	80%	20%
All pts	BP 1 n. 90 (60%)	42%	58%
eGFR ≥60 all BP 97	BP0 n. 57 (59%)	82%	18%
eGFR ≥60 all BP 97	BP1 n. 40 (41%)	72.50%	27.5
eGFR <60 all BP 54	BP0 n. 4 (7%)	25%	75%
eGFR <60 all BP 54	BP1 n. 50 (93%)	18%	82%
GGS 0% all BP 53	BP0 n. 34 (64%)	85%	15%
GGS 0% all BP 53	BP1 n. 19 (36%)	79%	21%
GGS≥20% all BP 34	BP0 n. 2 (6%)	50%	50%
GGS≥20% all BP 34	BP1 n. 32 (94%)	22%	78%
TID sc. 0 all BP 39	BP0 n. 24 (62%)	96%	4%
TID sc. 0 all BP 39	BP1 n. 15 (38%)	53%	47%
TID sc.4-6 all BP 27	BP0 n. 2 (7%)	Not valuable	Not valuable
TID sc.4-6 all BP 27	BP1 n. 5 (93%)	4%	96%
AH score0 all BP 86	BP0 n. 48(56%)	85%	15%
AH score0 all BP 86	BP1 n. 38 (44%)	14%	86%
AH sc. 2-3 all BP 15	BP0 n. 1(7%)	Not valuable	Not valuable
AH sc. 2-3 all BP 15	BP 1 n. 14(93%)	14%	86%

In eGFR ≥ 60 ml/min/1.73 m2 the patients are 97: BP 0 n. 57 (59%) and BP 1 n. 40 (41%); in BP 0 "no progr" is 82% and "progr" 18%; in 40 patients BP 1 "noprogr " is 72.5% and "progr" 27.5%. In eGFR < 60 ml/min the patients are 54: BP 0 are n. 4 (7%) and BP 1 are n. 50 (93%); in the 4 BP 0 "noprogr" is 25% and "progr" 75%; in the 50 patients BP 1 "no progr" is 18% and " Progr" is 82% (Table 3).

Outcome in BP0 and BP1 patients according to percentages of global glomerular sclerosis (GGS 0% versus GGS ≥ 20%).

The patients with GGS 0% (n. 53) were compared with patients with GGS ≥ 20% (n. 34). In patients with GGS 0% (n.53) the BP 0 are 34 (64%) and BP 1 19 (36%); the 34 BP 0 show 85% of "noprogr" and 15 % progr". The 19 BP1 show: 15 (79%) of "noprogr" and 4 (21%) of "progr". In patients with GGS ≥ 20% (n. 34) the BP 0 are 2 ((6%) and BP1 are 32 (94%); the 2 BP 0 show 1 "noprogr" (50%) and 1 "progr" (50%); the 25 BP1 patients show 78% of "noprogr" and (22%) of "progr".

Outcome in BP0 and BP1 patients according to value of TID score [0 (absent) versus tubular atrophy, interstitial fibrosis and inflammatory cell infiltration diffuse (score 4-6)].

The patients with absent Tubulo-Interstitial Damage (TID score: 0, n. 39) were compared with patients with focal or diffuse tubular atrophy, interstitial fibrosis and inflammatory cell infiltration (TID score: 4-6, n. 27). In patients with TID 0 the BP 0 are 24 (62%) and BP1 15 (38%); the 24 BP 0 show 96% of "noprogr" and 4% of "progr"; the 15 BP1show 53% of "noprogr" and 47% of "progr". In patients with TID score 4-6 BP 0 are 2 (7%) and the BP 1 are 25 (93%): the BP 0 Show 0% of "noprogr" (0%) and 1 (100%) of "progr"; the BP1 show 4% of "no progr" and 96% of "progr". Thus, the functional outcomes are rather different as in the BP1 patients with TID score 0 "progr" is 47%, while in BP1 patients with TID score 4-6 the "progr" is 96%.

Outcome in BP0 and BP1 patients according to value of AH (arteriolar hyalinosis) absent (0) and arteriolar hyalinosis diffuse (2) and diffuse with lumen reduction (3).

In patients with AH score 0 the patients are n. 86 with BP 0 is n. 48 (56%) and BP 1 n. 38 (44%): the 48 BP 0 patients show 41 (85%) of "no progr" and 7 (15%) of "Progr". In patients with BP 1 (n.38) "noprogr" is 22 (58%) and "progr" is 16 (42%). In patients with AH score 2-3 (2: diffuse arteriolar hyalinosis, 3: diffuse arteriolar hyalinosis with lumen reduction) BP 0 are 2 (outcome not valuable); the BP1 patients are n. 14: "noprogr" n. 2 (14%) and "Progr." n. 12 (86%). **Outcome in BP 0 and BP 1 patients according to the groups of combined urinary excretion of IgG/C & α2m/C (0+0, 0+1, 1+0, 1+1).**

The 0+0 group in combination with BP0 and with Steroids and Cyclophosohamide treatment (n. 15 patients) show 100% of "noprogr" and 0% of "progr". The 1+1 group in combination with BP1 and Steroids and Cyclophosphamide treatment (n.14 patients) "noprogr" is 0% and "progr." is 100%. In the groups 0+1 and 1+0 (n. 55 patients) treated with Steroids and Cyclophosphamide "noprogr" are 32 patients (58%) and "progr" are 23 (42%).

Discussion

In 151 patients with GN and NS the percentage of normal Blood Pressure (BP 0) is lower [n. 61 (40%)] than that of high Blood Pressure (BP 1) [n. 90 (60%)]. The percentages of BP 0 and BP 1 are influenced by level of renal function (eGFR ≥ or < 60 ml/min) with increase of percentages of BP 0 in patients with eGFR ≥ 60 ml/min (59%) and increase of percentages of BP 1 (93%) in patients with eGFR < 60 ml/min. These variations in percentages of BP 0 and BP 1 changes the outcome: "noprogr" is reduced from 42% to 18% in BP 1 patients associated with eGFR < 60 ml/min and "progr" increases from 58% to 82% in BP 0 associated with eGFR ≥ 60ml/min. Similar observations by comparison of GGS 0% with GGS ≥ 20% that show a reduction of "noprogr" from 42% to 22% and increases the percentage of "progr" from 58% to 78%. Similar observations evaluating TID score and AH score. These data show that the functional outcome in BP 0 and BP 1 is dependent on association with functional, Proteinuric and histologic parameters. This observation allow to suggest that the combination in every patient of BP with eGFR, GGS%, TID score and AH score may be a predictor functional outcome at diagnosis (for example prediction of ESRD) and this prediction may influence the choice of treatment.

Conclusions

Considering only the percentage of normal blood pressure (BP 0, n. 61) and high blood pressure (BP 1, n 90) as such in 151 patients with GN and NS the BP 0 patients show better outcome: "noprog." 80% and "Progr." 20%, while in BP 1 patients "no Progr." is 42% and "Progr" 58%. The highest percentage of "noprogr" are observed in BP 0 associated with eGFR ≥ 60 ml/min ("noprogr" 82%), GGS 0%("noprogr" 85%), TID score 0 ("noprogr" 96%) and AH score 0 ("noprogr" 85%). The highest percentages of "progr" are observed in BP1 patients associated with eGFR <60 ml/min ("progr" 82%), TID score 4-6 ("progr" 96%) and AH score 2-3 ("progr" 86%). Thus the most powerful parameters associated with worse renal function are eGFR <60, TID score 4-6 and AH score 2-3. These results show that outcome of BP 0 and BP 1 patients are associated with eGFR < *vs.* ≥ 60 ml/min, TID score 0 *vs.* 4-6 and AH score 0 *vs.* 2-3. In every single patients, the combination at diagnosis of these 4 parameters may be able to predict the functional outcome and suggest that patients whose combination predict ESRD should not treated with immunosuppression.

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