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ASYMPTOMATIC CAROTID ARTERY STENOSIS IN PATIENTS WITH PRIMARY CHRONIC GLOMERULONEPHRITIS

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Summary. *Cardiovascular complications are the leading cause of morbidity and mortality in renal patients (p). Atherosclerosis is the major factor responsible for death-threatening events, such as myocardial infarction and stroke. Asymptomatic carotid artery stenoses (ACASs) are an important predictor of atherosclerotic involvement, not only in the brain, but also in other vascular territories (heart, lower limbs).*
The study was conducted prospectively on 3 groups of p matched by sex and age, with primary chronic glomerulonephritis (CGN), essential hypertension (EHT) and normal controls (NC). Exclusion criteria were diabetes mellitus and symptoms or history of cerebrovascular disease. All p were assessed concerning the major risk factors (RF): blood pressure (BP), cholesterol (C), LDL-C, HDL-C, triglycerides (T), serum creatinine (SC), proteinuria (P), fibrinogen (F), leukocytes (L), smoking habits. ACASs were diagnosed by means of an extracranian velocimeter Doppler with spectral analysis. All p underwent ECG and an exercise ECG when necessary, to identify concomitant coronary heart disease (CHD). Peripheral vascular disease (PVD) was proven clinically and by Doppler scan.
The prevalence of ACASs was 32.51% in p with CGN (in p with NS - 25%; NS+CRF - 42.92%); 20.25% in EHT; 7.89% in NC. The degree of ACASs was in the range of grades II - III in all groups. More significant cerebrovascular RF were found in group 1 than in groups 2, 3 for: age ($P < 0.001$), F ($P < 0.001$), L ($P < 0.001$), proteinuria ($P < 0.01$), smoking ($P < 0.001$), HT ($P < 0.0001$), SC ($P < 0.001$), C ($P < 0.001$), LDL-C ($P < 0.0001$), T ($P < 0.001$), male gender ($P < 0.01$). The stenosis index correlated strongly with the following RF: age, SBP, LDL-C, F, SC, proteinuria in groups 1; with SBP, LDL-C, age in group 2 and group 3, respectively. Of the p with CHD, 39.13% presented ACASs and of the p with PVD, 84.37% presented ACASs (group 1).
The prevalence of ACASs is far more significant in p with CGN and is strongly related to cerebrovascular RF. Mild and moderate ACASs overcome severe ACASs and are highly significant in p with nephrotic syndrome and chronic renal failure. ACASs p associate frequently CHD and PVD. Extracranian ultrasound Doppler should be recommended as routine examination in p with CGN in order to reveal ACASs in early stages.

Key words: *Asymptomatic carotid artery stenosis, cerebrovascular risk factors, coronary heart disease, Doppler ultrasonography, peripheral vascular disease, chronic glomerulonephritis*

Introduction

Cardiovascular complications are the leading cause of morbidity and mortality in renal patients, especially in end-stage renal disease patients (1). Atherosclerosis is the major factor responsible for death-threatening events, such as myocardial infarction and stroke. Over the last years, basic and clinical research has brought new insights into the pathogenesis of atherosclerosis. Attention has focused on metabolic and mechanical factors of vascular remodelling associated with atherosclerotic plaques (2).

There is a large body of evidence that highlights the primary importance of physical factors (of which hypertension is the most important), metabolic and humoral factors, as well as of vasoactive, endothelium - and platelet - derived compounds, disturbances of calcium and phosphorus metabolism and cytokines, in the complex process of atherosclerosis (2, 3). More recently, apart from classic risk factors, vitamin E deffiiciency and elevated C-reactive protein levels are associated with an increased intima-media thickening, while

small molecular weight apo (a) isoforms and increased levels of oxidized low-density lipoprotein are strongly connected with the presence of carotid plaques (4).

Due to the combination of atherogenic risk factors, chronic renal failure (CRF) patients are at high risk of atherosclerosis and of developing later on in their evolution major vascular events in crucial territories, such as the heart and the brain (5). It has been generally assumed that CRF patients, either on conservative management or on renal replacement therapies, represent an important cathegory of patients prone to develop atherosclerotic lesions in the coronary and carotid arteries, as well as in the peripheral arteries. Of these patients, those with chronic glomerulonephritis (CGN) deserve a special attention for many reasons. Firstly, it is well known that these patients form an important group of strong candidates for renal replacement therapies in the long run and, therefore, sum up the great majority of cardio- and cerebrovascular risk factors. In addition, it is of note that certain particularities occur, such as the variability of the lipid abnormalities in the nephrotic syndrome and the fact that these changes are combined with those specific for CRF. Moreover, proteinuria should not be overlooked as a potential atherosclerosis risk factor.

Carotid artery lesions have been studied in predialysis patients (6) and in patients on maintenance hemodialysis (7).

These studies revealed a high prevalence of carotid plaques in CRF patients when compared to control patients. Also, the study of Rossi et al., as well as other studies, stress the extension of the atherosclerotic lesions to other important vascular beds, namely the coronary arteries and the peripheral arteries (3, 6, 8).

From the practical standpoint, it is worth pointing out that asymptomatic carotid artery stenoses (ACASs) are an important predictor of further atherosclerotic involvement and offer a genuine vascular window with regard to other vascular territories. There are studies that support this aspect and evidence an increased incidence of carotid stenoses in patients who present atherosclerotic complications (ischaemic heart disease, peripheral vascular disease) (9).

To the best of our knowledge, up to now, no study was carried out in patients with CGN with regard to the abovementioned issues. The purpose of our study was to establish by extracranian Doppler ultrasonography (US), the prevalence of ACASs in primary CGN patients, in relationship with the major cerebrovascular risk factors (RF): age, serum cholesterol, serum triglycerides, hypertension, leukocytes, smoking, serum creatinine and proteinuria. Also, we evaluated the association between ACASs and other forms of atherosclerotic disease (coronary heart disease - CHD and peripheral vascular disease - PVD).

Subjects and Methods

Study design

The study was conducted prospectively on three groups of patients (p) matched by sex and age, with primary CGN, essential hypertension (EHT) and normal controls (NC). Exclusion criteria were diabetes mellitus and symptoms or history of cerebrovascular disease. Group 1 - primary CGN p, comprised 83p, group 2 - EHT p, consisted of 79 p and group 3 - NC, which comprised 76 subjects. Group 1 was divided in 4 subgroups: subgroup A - CGN+nephrotic syndrome (NS); subgroup B - CGN+NS+CRF; subgroup C - CGN+CRF; subgroup D - CGN. All patients were assessed concerning age, blood pressure (determined in mmHg) (systolic blood pressure - SBP, diastolic blood pressure - DBP, the duration of HT in years); serum cholesterol (C), LDL-C, HDL-C, serum triglycerides (T), serum creatinine (SC), fibrinogen (F), by standard auto-analyzer technique Axsym (mg%); proteinuria was evaluated by the Biuret method (g/24h); leukocytes were measured by standard methods (elements/mm^3); smoking habits were assessed by a standard questionnaire (pack-years). ACASs were diagnosed by means of an extracranian velocimeter Doppler (Explorer CVC - DMS - Montpellier, France) with fast-Fourier transformation spectral analysis, using a 4 MHz CW (continuous wave) probe. The extracranial carotid artery system was explored, namely the internal carotid artery (ICA) and the external carotid artery (ECA), bilaterally. The severity of ACASs (grade of stenosis - stenosis index - STI) was appreciated as follows (10): Grade I - < 23% (diameter reduction with presence of peak systolic velocity of 100 cm/s); grade II - 23-40%; grade III - 40-50%; grade IV - 50-70%; grade V - > 70%. All examinations were performed by the same operator (MP), who had no other previous contact with the patients.

To identify concomitant CHD, all p and normal subjects underwent clinical evaluation, an electrocardiogram and an exercise electrocardiogram, when necessary. PVD was diagnosed clinically and by Doppler velocity scan in all groups.

Statistical analysis

Clinical, biochemical and Doppler US data were evaluated by statistical methods using the EPI INFO 6, INSTAT and EXCEL Statistical Packages: comparison between clinical and biochemical data in the three groups (expressed as means ± SEM) by unpaired Student's t-test and one-way ANOVA analysis; the prevalence of $ACAS_s$ was expressed in % and comparison between prevalences was performed by Z test; risk factors were assessed by odds ratio (95% CI) and their prevalence in $ACAS_S$ p when compared to p without $ACAS_S$ was evaluated by Z test; the correlations between the stenosis index (STI) and the cerebrovascular RF were performed by linear regression analysis (parametric single Pearson's test); for the evaluation of independent RF, multiple regression analysis was used. Correlation coefficients (r and RR values) of the linear regression analysis and the multiple regression analysis, respectively, are presented in relationship with P values. Statistical significance was considered as $P < 0.05$.

Results

Assessment of clinical and biological data

A comparison between clinical and biological data in groups 1, 2, 3 is presented in Table 1, and in subgroups A, B, C, D in Table 2.

Assessment of $ACAS_S$

The prevalence of $ACAS_S$ in group 1(primary CGN) was 32.51% (27p; M-70.37%; F-29.63%); monolateral ICA stenoses – 24.1%; bilateral ICA stenoses – 6%; ICA + ECA stenoses – 2.4%. The severity of stenoses, according to the classification of Touboul (10), was as follows: grade II – 12p (14.46%); grade III – 9p (10.84%); grade IV – 4p (4.82%); grade V – 2p (2.41%). *The prevalence of $ACAS_S$ in the subgroups of group 1* was: subgroup A (CGN + NS) – 4p(25%); subgroup B (CGN + NS + CRF) – 12p (42.92%); subgroup C (CGN + CRF) – 8p(36.46%); subgroup D (CGN) – 3p(17.61%). The prevalence comparison between the subgroups (Z test) showed the following significance: A-B ($P < 0.05$) A-C (not significant NS); A-D (NS); B-C (NS); B-D ($P < 0.05$); C-D ($P<0.05$).

The prevalence of $ACAS_S$ in group 2 (EHT) was 20.25% (16p; M-68.75%; F-31.25%); all monolateral ICA stenoses, which disclosed the following grades of severity:- grade II – 9p (11.39%); grade III – 5p (6.33%); grade IV – 2p (2.53%).

Table 1. Clinical and biological parameters of patients in groups 1, 2, 3.

		Group 1	Group 2	Group 3	Gr. 1 - 2	Gr. 1 - 3	Gr. 1 - 2 - 3
Nr. patients		83	79	76			
Age (y)		52.7 ± 10.2	54.3 ± 11.7	51.9 ± 7.2	NS	NS	NS
Sex	M (%)	65.06	60.75	60.52	NS	NS	–
	F (%)	34.94	39.25	39.48	NS	NS	–
Body mass index (BMI)		22.9 ± 2.5	25.7 ± 2.9	26.1 ± 1.3	P < 0.0001	P < 0.0001	P < 0.0001
Hypertension (%)		78p (93.97%)	79p (100%)	0	NS	_	–
Smokers (%)		38p (45.78%)	36p (45.56%)	37p (48.68%)	NS	NS	–
Past smokers (%)		24p (28.91%)	23p (29.11%)	20p (26.31%)	NS	NS	–
Non-smokers (%)		21p (25.30%)	20p (25.31%)	19p (25%)	NS	NS	–
Cholesterol (mg%)		245.13 ± 60.12	230.45 ± 41.61	208.11 ± 11.51	P = 0.0663	P < 0.0001	P < 0.0001
HDL cholesterol (mg%)		40.08 ± 13.72	27.05 ± 10.15	19.98 ± 8.17	P < 0.0001	P < 0.0001	P < 0.0001
LDL cholesterol (mg%)		162.24 ± 35.56	143.34 ± 38.89	131.13 ± 32.12	P = 0.0011	P < 0.0001	P < 0.0001
Triglycerides (mg%)		173.34 ± 110.87	141.17 ± 69.45	137.78 ± 73.34	P = 0.0289	P = 0.0172	P = 0.0162
Fibrinogen (mg%)		478.76 ± 153.15	330.08 ± 105.56	320.08 ± 103.14	P < 0.0001	P < 0.0001	P < 0.0001
Serum creatinine (mg%)		6.2 ± 3.7	1 ± 0.1	0.9 ± 0.1	P < 0.0001	P < 0.0001	P < 0.0001
Proteinuria (g/24h)		3.2 ± 1.8	0.22 ± 0.1	0.1 ± 0.03	P < 0.0001	P < 0.0001	P < 0.0001
Leucocytes (elem/mm3)		10500.88 ± 2300.43	7200.22 ± 1500.79	6900.08 ± 800.13	P < 0.0001	P < 0.0001	P < 0.0001
HT	SBP (mmHg)	162.26 ± 14.83	154.64 ± 15.34	–	P = 0.0006	–	–
	DBP (mmHg)	89.95 ± 5.08	83.34 ± 9.08	–	P < 0.0001	–	–
	Duration (y)	11.6 ± 6	10.3 ± 4	–	NS	–	–

Clinical and biological data are expressed as means ± SEM; comparison between groups 1-2 and groups 1-3 (unpaired Student's t-test); comparison between groups 1-2-3 (one-way ANOVA analysis); statistical significance was considered as $P < 0.05$.

Table 2. Clinical and biological parameters of patients in the subgroups of group 1 – CGN (A, B, C,D).

		Group 1	Group 2	Group 3	Gr. 1 - 2	Gr. 1 - 3
Subgroup		CGN+NS	CGN+NS+CRF	CGN+CRF	CGN	
Nr. patients		16	28	22	17	
Age (y)		48.9 ± 8.5	54.8 ± 6.7	55.2 ± 10.4	52.04 ± 9.6	NS
Sex	M (%)	62.5	64.28	63.63	58.82	–
	F (%)	37.5	35.72	36.37	41.18	–
Hypertension		15p (93.73%)	28p (100%)	22p (100%)	13p (76.47%)	–
Smokers (%)		10p (62.5%)	13p (46.42%)	4p (18.18%)	11p (64.70%)	–
Past smokers (%)		6p (37.5%)	6p (21.42%)	4p (18.18%)	8p (47.05%)	–
Non-smokers (%)		4p (25%)	7p (25%)	8p (36.36%)	2p (11.76)	–
Cholesterol (mg%)		271.12 ± 81.33	310.34 ± 62.87	322.22 ± 58.45	239.77 ± 28.23	P = 0.0002
HDL cholesterol (mg%)		36.33 ± 18.87	18.55 ± 21.43	21.65 ± 26.32	27.44 ± 13.34	P = 0.0536
LDL cholesterol (mg%)		186.11 ± 39.79	198.23 ± 42.64	220.05 ± 36.79	166.76 ± 18.46	P = 0.0003
Triglycerides (mg%)		221.09 ± 46.19	243.17 ± 57.38	239.28 ± 62.63	221.89 ± 62.47	NS
Fibrinogen (mg%)		549.53 ± 110.07	579.12 ± 119.38	581.36 ± 103.75	559.67 ± 122.12	NS
Serum creatinine (mg%)		1.1 ± 0.3	8.7 ± 1.0	8.4 ± 0.7	1.2 ± 0.2	P < 0.0001
Proteinuria (g/24h)		3.1 ± 1.6	4.6 ± 1.7	4.3 ± 0.8	3.6 ± 1.9	P = 0.0121
Leucocytes (elem/mm3)		11500.22 ± 5200.38	14300.95 ± 3800.44	13800.37 ± 1600.5	9200.34 ± 2100.78	P < 0.0001
HT	SBP (mmHg)	160.15 ± 12.17	163.78 ± 18.19	165.37 ± 16.48	159.08 ± 11.47	NS
	DBP (mmHg)	89.7 ± 6.3	91.64 ± 7.51	90.08 ± 4.12	86.64 ± 3.83	P = 0.0587
	Duration (y)	11.8 ± 8	12.3 ± 6	11.7 ± 3	10.9 ± 5	NS

Clinical and biological data are expressed as means ± SEM; comparison between subgroups A, B, C, D (one-way ANOVA analysis); statistical significance was considered as $P < 0.05$.

The prevalence of ACASs in group 3 (NC) was 7.89% (6p - M - 83.33%, F - 16.67%), with monolateral ICA stenoses. Their severity was: grade II - 3p (3.94); grade III - 2p (2.63%); grade IV - 1p (1.32%).

The prevalence comparison between groups 1-2 (Z test) showed a statistical significance of $P < 0.05$, and between groups 1-3 of $P < 0.01$, respectively.

Evaluation of cerebrovascular risk factors (RF)

The evaluation of cerebrovascular RF was performed in all three groups of p, using the odds ratio method (95% CI) and is presented in Tables 3, 4 and 5. In group 1, multiple regression analysis showed as independent RF: systolic blood pressure, LDL-C, age, HDL-C, fibrinogen, male gender and smoking (Table 6).

Table 3. Risk factors for cerebrovascular disease (ACASs) in group 1

Risk factor	Odds ratio (95% CI)
1. Age	7.14 (4.84 - 64.62)
2. Hypertension	6.21 (4.33 - 52.31)
3. Cholesterol	5.92 (4.33 - 54.43)
4. Smoking	5.23 (4.53 - 22.16)
5. Serum creatinine	5.14 (1.68 - 16.33)
6. LDL cholesterol	4.84 (4.15 - 44.38)
7. Leucocytes	4.59 (1.55 - 13.88)
8. Proteinuria	4.21 (1.33 - 14.82)
9. Fibrinogen	3.93 (3.78 - 46.05)
10. Triglycerides	2.83 (2.33 - 37.43)
11. Male gender	2.71 (2.12 – 21.40)

Table 4. Risk factors for cerebrovascular disease (ACASs) in group 2

Risk factor	Odds ratio (95% CI)
1. Age	6.41 (4.37 - 49.77)
2. Smoking	6.23 (2.57 - 64.49)
3. LDL cholesterol	6.23 (3.21 - 41.74)
4. Cholesterol	5.88 (3.43 - 36.96)
5. Triglycerides	5.86 (3.12 - 56.05)
6. Male gender	4.35 (2.89 – 35.81)

Table 5. Risk factors for cerebrovascular disease (ACASs) in group 3

Risk factor	Odds ratio (95% CI)
1. Age	6.32 (3.86 - 26.71)
2. LDL cholesterol	6.12 (2.10 - 28.90)
3. Cholesterol	5.86 (3.68 - 31.71)
4. Smoking	4.75 (1.48 - 42.21)
5. Triglycerides	4.20 (2.03 - 33.81)
6. Male gender	3.75 (1.98 – 23.18)

Table 6. Independent risk factors for ACASs in patients with CGN

Independent risk factors	Relative risk (95% CI)	P value
Systolic blood pressure	1.28 (1.05-1.31)	0.012
LDL cholesterol	1.11 (1.02-1.18)	0.024
Age	1.34 (1.10-1.45)	0.001
HDL cholesterol	0.89 (0.72-1.01)	0.006
Fibrinogen	1.18 (1.06-1.23)	0.05
Smoking	1.43 (1.24-1.62)	0.001
Male gender	1.23 (1.02-1.14)	0.05

Multiple regression analysis; significance was considered as $P<0.05$

A comparison with regard to these cerebrovascular RF was performed in p with and without ACASs, in each of the three groups (Z test). The results in group 1 revealed a significantly higher proportion of p who presented ACASs in relationship with the following RF: age ($P < 0.001$); fibrinogen ($P < 0.001$); leukocytes ($P < 0.001$); proteinuria ($P < 0.01$); smoking ($P < 0.001$); hypertension ($P < 0.0001$); serum creatinine ($P < 0.001$); serum cholesterol ($P < 0.001$); serum triglycerides ($P < 0.001$); male gender ($P < 0.01$).

In group 2, ACASs+p overcame the number of p without ACASs according to the following RF: smoking ($P < 0.001$); age ($P < 0.001$); serum cholesterol ($P < 0.0001$); serum triglycerides ($P < 0.0001$); male gender ($P < 0.01$), whereas in group 3, ACAS+p overran ACAS-p for age ($P < 0.05$); smoking ($P < 0.05$); serum cholesterol ($P < 0.05$); serum triglycerides ($P < 0.05$); male gender ($P < 0.01$).

Linear regression analysis evidenced a strong direct correlation between the stenosis index (STI) and several cerebrovascular RF. In group 1, we found a highly significant correlation between the STI and age ($r = 0.66$; $P < 0.001$); SBP ($r = 0.74$; $P < 0.0001$); LDL-C ($r = 0.83$; $P < 0.0001$); fibrinogen ($r = 0.89$; $P < 0.0001$); serum creatinine ($r = 0.53$; $P < 0.01$); proteinuria ($r = 0.73$; $P < 0.0001$) (Fig. 1, 2, 3, 4, 5, 6). In group 2, linear regression analysis revealed a significant correlation between the STI and SBP ($r = 0.88$; $P < 0.01$); LDL-C ($r = 0.78$; $P < 0.01$); age ($r = 0.85$; $P < 0.01$), while in group 3, the STI correlated with LDL-C ($r = 0.73$; $P < 0.05$); age ($r = 0.88$; $P < 0.05$) and SBP ($r = 0.52$; $P < 0.05$).

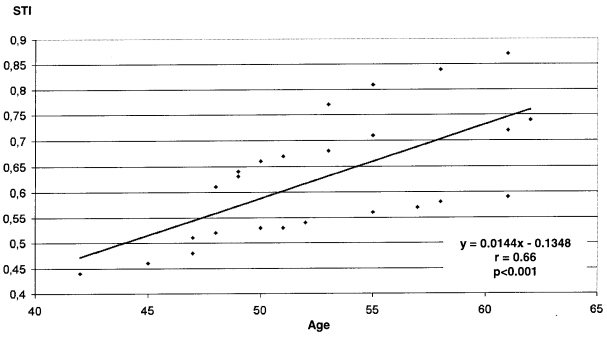

Fig. 1. Correlation between the STI and age in group 1 (linear regresion analysis).

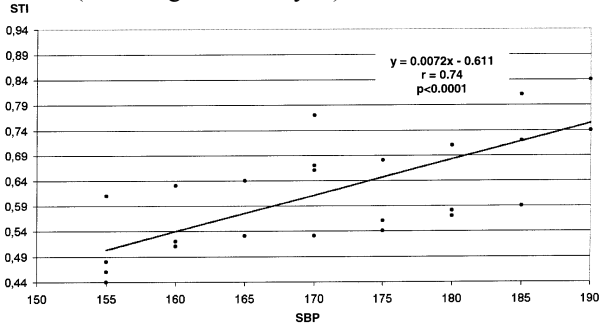

Fig. 2. Correlation between the STI and SBP in group 1 (linear regression analysis).

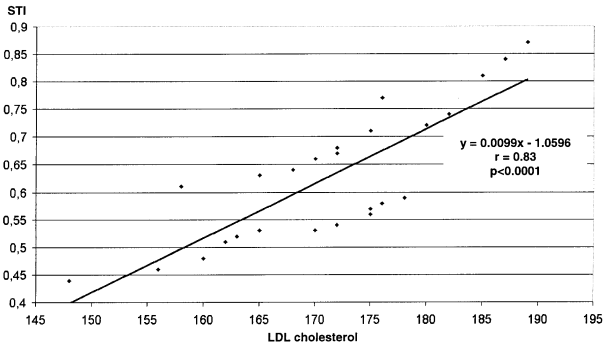

Fig. 3. Correlation between the STI and LDL-cholesterol in group 1 (linear regression analysis).

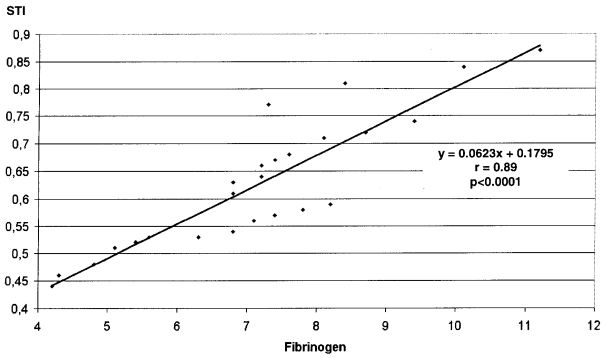

Fig. 4. Correlation between the STI and fibrinogen in group 1 (linear regression analysis).

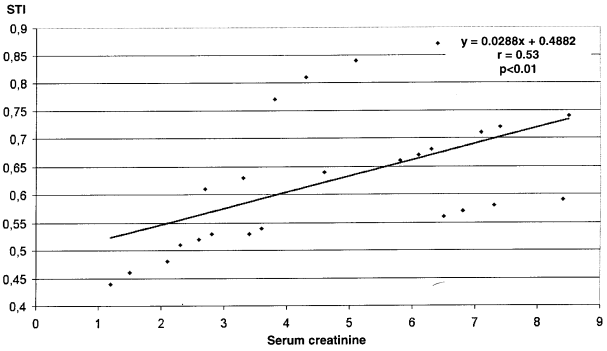

Fig. 5. Correlation between the STI and serum creatinine in group1 (linear regression analysis).

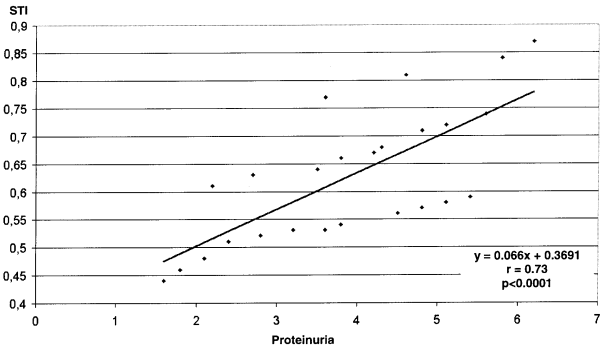

Fig. 6. Correlation between the STI and proteinuria in group 1 (linear regression analysis).

Association between coronary heart disease and peripheral vascular disease

CHD was diagnosed in 69p (83.13%) in group 1 (all forms of CHD), 43p (54.43%) in group 2 (all forms of CHD) and 11p (14.52%) in group 3 (silent myocardial ischemia).

In group 1, of the p with CHD, 39.13% presented $ACAS_S$ of variable grades; in group 2, of the p with CHD, 37.21% were recorded with ACASs and in group 3, 18.18% of p were diagnosed with ACASs (a very striking difference between groups 1-3; $P < 0.01$). *PVD* was found in 32 p (38.55%) in group 1, 18 p (22.78%) in group 2. No p of group 3 was diagnosed with PVD. In group 1, 84.37% of the p with PVD associated ACASs, while in group 2, 66.66% of the p with PVD presented ACASs, fact that deserves a certain attention ($P < 0.05$).

Discussion

The results of our study reveal a *prevalence of ACASs* of 32.51% in CGN patients vs. 20.25% in EHT patients and 7.89% in healthy controls, respectively. It is of note that the prevalence of ACASs in CGN is far more significant than in the other two groups and that it is a more striking difference between group 1 and group 3. Furthermore, the comparison between the subgroups of group 1 disclosed a high prevalence of ACASs in subgroups B and C, with a relevant difference between subgroups A-B, B-D and C-D. These data point to the fact that group 1 and especially its subgroups B and C deal with patients that display a complex clinical and biological condition, namely they associate CGN with NS and CRF.

Other studies, performed with B-mode Doppler ultrasonography, revealed high prevalences of carotid artery lesions (CALs) due to atherosclerosis in patients on conservative management or on maintenance hemodialysis. Rossi A. et al. reported a prevalence of 62% CALs in CRF patients vs. 47% in normal controls, difference which was more significant between normotensive CRF patients and healthy subjects (62% vs. 19%) (6). Similar changes are stated in studies on hemodialysis patients: 73.8% carotid plaques vs. 44% in normal controls (7) and 72% carotid plaques vs. 32% in healthy controls (4).

Also, the same studies reveal the fact that the severity of CALs was in the range of grades II-III and that the vast majority of the patients presented with an extensive process of carotid artery atherosclerosis rather than with very severe stenosis (4, 6, 7).

This is in agreement with our data which show extensive mild and moderate ACASs in group 1 (bilateral ICA and ICA+ECA).

A vast array of *risk factors* (RF) has been demonstrated in all three groups, but in group 1 there are certain additional RF and, thus, they deserve a special attention.

Age is by far one of the most important independent RF for atherosclerosis, proven equally in groups 1, 2 and 3. Irrespective of age, *male gender* was also a leading RF in all patients. There was a strong direct correla-

tion between age and the STI in all groups. Several studies report similar data with regard to age and male gender (3, 4, 5, 6, 7).

Hypertension (HT) is a well known independent RF for atherosclerosis and of major vascular events, its duration being of primary importance. It was demonstrated as an important RF in groups 1 and 2, in which SBP was an independent RF which correlated with the severity of ACASs. These data are in keeping with those presented by other works. There is debate as to whether SBP or DBP is more dangerous in the long run. Some authors underline the fact that the high values of SBP are a stronger predictor of severe and extensive atherosclerotic lesions than those of DBP (5, 7), while other authors claim that neither the values nor the duration of HT are of predictive value (3, 4). Rossi A. et al. found that the prevalence of CALs was the same in hypertensive patients and normotensive patients in the CRF group and that there was a greater difference in the prevalence of CALs between normotensive patients (than between hypertensive patients) of the CRF group when compared to NC. The authors draw the conclusion that HT is not the discriminating factor and that uremia per se might induce an accelerated atherosclerosis (6).

Lipid abnormalities in NS and CRF have been postulated to contribute to the high prevalence of major cardio- and cerebrovascular accidents. CRF patients have elevated levels of total cholesterol, LDL-cholesterol and triglycerides, while the levels of HDL-cholesterol are low (3, 4, 6, 7).

Hyperlipidemia in nephrotic syndrome patients is characterized by increased very low density lipoprotein (VLDL), LDL-cholesterol and lipoprotein (a) levels, with little change in HDL-cholesterol (11, 12).

High levels of total serum cholesterol, serum triglycerides and LDL-cholesterol and decreased levels of HDL-cholesterol have been recorded in group 1, with milder impairment of these biological data in groups 2 and 3. Of these changes, LDL-cholesterol and HDL-cholesterol proved to be the strongest independent RF, which also correlated with the STI. The most important abnormalities of the lipid profile were diagnosed in subgroups B and C, which associated the lipid modifications due to NS with those present in CRF.

Smoking was of particular interest in all groups of patients, proven as a strong predictive RF for ACASs and documented as an independent RF in CGN patients. These data coincide with those obtained in other studies performed on CRF patients (3, 4, 5). Fibrinogen and hyperhomocysteinemia have been discussed very often in association with cigarette smoking (5).

Another important independent RF for ACASs was *fibrinogen*, which presented high levels in CGN patients. According to other studies, fibrinogen was related to the extension of vascular lesions in CRF patients, as well as to the degree of carotid stenoses (6). Furthermore, malnourished patients had significantly elevated fibrinogen levels, being an indicator of an ongoing inflammatory process (4). In this setting, it is worth mentioning that our CGN patients with decreased body mass index had a proportionally increased level of plasma fibrinogen.

Also, another remarkable issue would be the undeniable relation between increased fibrinogen levels and endothelial dysfunction, concomitantly with blood coagulation abnormalities (5, 13). Attention has focused on *leukocytes*, their total number being significantly increased in renal patients, especially in the course of CRF (6). Leukocytes are of particular interest, their role in atherogenesis being well known (14). In our study, CGN patients revealed increased values of leukocytes, which acted as RF for ACASs. In the study of Rossi A. and coworkers, white blood cell count was found to be positively correlated with CALs severity in CRF patients (6).

Today it is common knowledge that *serum creatinine* and other catabolic azotemic products may have a causative role in atherogenesis. Many studies support this idea in CRF patients in pre-dialysis stage or on renal replacement therapies (3, 7). We found serum creatinine as an important RF for ACASs in group 1 patients who associated CRF with CGN. This finding is quite challenging and was demonstrated in several works, in non-renal patients, namely in patients with carotid stenoses who have previously had transient ischaemic attacks (15) and in a general population of middle-aged men (16). The results of these studies indicated that elevated serum creatinine may be an independent predictor of cerebrovascular disease in both normotensive and hypertensive subjects. What is most surprising, even values of serum creatinine within the range of upper normal or mildly elevated levels are related to the angiographic severity of internal carotid artery disease in patients who have previously had transient ischaemic attacks (15).

An elevated serum creatinine level may be a marker for subtle renal damage as a consequence of raised blood pressure and may constitute an additional risk factor for cerebrovascular disease (16).

At present *proteinuria* is accepted as a considerable RF for atherosclerosis. In our study, proteinuria correlated strongly with the STI and was demonstrated as an important RF for ACASs in CGN patients, especially in those who present nephrotic syndrome with heavy proteinuria.

One aspect of the role of proteinuria in the pathogenesis of atherosclerosis is related to its contribution to endothelial dysfunction. It has been suggested that either hipoalbuminemia itself or other aspects of the dyslipidemia characteristic of nephrotic syndrome might impair endothelial function, irrespective of the blood pressure values. These changes were ascribed to increased levels of LDL-cholesterol and triglycerides, which are associated with impaired nitric oxide-mediated vasodilatation (17). Of interest, hipoalbuminemia, as a direct consequence of heavy proteinuria, has been associated to a high prevalence of carotid plaques (8). Other studies failed to demonstrate a correlation between CALs and proteinuria, probably due to its low values in CRF patients (6).

Our present study evidenced a high prevalence of

coronary heart disease (CHD) and *peripheral vascular disease* (PVD) associated with ACASs in CGN patients, fact that ascertains the extension of the process of atherosclerosis in the main vascular beds, such as the heart, brain and lower limbs in this particular cathegory of patients.

CHD has been described in close relationship with ACASs in renal, as well as in non-renal patients, who are screened very often for ACASs before cardiac surgical procedures for coronary heart disease (18, 19).

Also, it has been shown that ACASs have been frequently associated to *PVD* (20, 21, 22).

Studies performed on renal patients revealed similar results. A study conducted on CRF patients disclosed the fact that all CRF patients with peripheral vascular disease and 86% of the patients with coronary heart disease had CALs (6). Kawagishi T. et al. showed that hemodialysis patients presented advanced atherosclerosis in the carotid and femoral arteries when compared with age-matched healthy control subjects (3). The same results were reported by Savage T. et al in dialysed CRF patients who presented a strong association between carotid artery lesions and femoral arteries atherosclerosis (71% of the CRF patients vs. 21% of controls) (8). All patients screened for carotid stenoses, coronary heart disease and peripheral vascular disease, were also subjected to biological investigations which revealed the classic risk factors for atherosclerosis. Our study draws the attention to this possible association and points to the fact that the great majority of the CRF patients, especially those with CGN, might overlap multiple vascular lesions in critical territories.

The ACAS study (Asymptomatic Carotid Atherosclerosis Study) shows the importance of detection of ACASs (23). Also, it has been underlined that the risk of stroke is multiplied by two or three in symptomatic stenoses in comparison with those which are asymptomatic (24), but one should not overlook the fact that the risk of brain infarction is 3-4% in asymptomatic stenoses (9, 25) and that 2.3% of asymptomatic stenoses carry a risk of ipsilateral stroke (23, 26). The narrower the stenoses, the more the risk of stroke is multiplied (27).

In conclusion, the present study provides evidence of an undeniable higher prevalence of ACASs in primary CGN patients when compared to EHT patients and, more strikingly, with normal controls. As cerebrovascular risk factors we demonstrated age, male gender, hypertension, lipid abnormalities, fibrinogen, leucocytes and, more interestingly, proteinuria and serum creatinine. The synergism of these risk factors explains the higher prevalence, the severity and the extension of atherosclerotic ACASs in primary CGN patients. The results of our study prove that extracranian Doppler ultrasonography is an accurate, non-invasive, reproducible method in the diagnosis of ACASs in these patients. This method is comparable with ECG and exercise ECG in terms of accuracy of diagnosis (28). It becomes patently obvious that in multivascular affected patients, not only does this method diagnose ACASs, but it also provides information with regard to a possible extension of the atherosclerotic disease to the coronary and peripheric vascular beds. Therefore, it should be kept in mind that extracranian Doppler ultrasonography becomes mandatory in CGN patients along with tailored therapies directed towards the major risk factors for atherosclerosis, in order to prevent cerebrovascular events.

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ASIMPTOMATSKA STENOZA KAROTIDNE ARTERIJE U BOLESNIKA SA PRIMARNIM GLOMERULONEFRITISOM

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Kratak sadržaj: *Kardiovaskularne komplikacije su vodeći uzrok morbiditeta i mortaliteta u bubrežnih bolesnika. Ateroskleroza je glavni faktor odgovoran za po život opasna stanja kao što su infarkt miokarda i šlog. Asimptomatske stenoze karotidne arterije (ACAS) su značajne za procenu raširenosti ateroskleroze, ne samo u mozgu već i u drugim organima i tkivima (srce, donji udovi).*
Ovo ispitivanje je učinjeno prospektivno na tri grupe pacijenata, sličnog pola i uzrasta, i to obolelih od primarnog hroničnog glomerulonefritisa (CGN), esencijalne hipertenzije (EHT) i zdravih kontrola (NC). Iz ispitivanja su isključene osobe koje su imale šećernu bolest i simptome ili anamnestičke podatke o cerebrovaskularnom oboljenju. Svi bolesnici su ispitivani u odnosu na glavne faktore rizika (RF): krvni pritisak (BP), holesterol (C), LDL-C, HDL-C, trigliceride (T), serum kreatinin (SC), proteinuriju (P), fibrinogen (F), leukocite (L) i pušenje. ACAS su dijagnostikovane pomoću ekstrakranijalnog Dopplera sa spektralnom analizom. Svim bolesnicima urađen je ECG, a EKG u testu opterećenja ako je to bilo potrebno da bi se potvrdila koronarna bolest (CHD). Periferno vaskularno oštećenje (PVD) dokazivano je klinički i upotrebom Dopplera.
Prevalenca ACAS bila je 32.5% u bolesnika sa CGN (u bolesnika sa NS - 25%, NS+CRF 42.92%); 20% u EHT; 7.89% u NC. U svim grupama stepen oštećenja je bio II-III. Značajniji cerebrovaskularni faktori rizika nađeni su u grupi 1 nego u grupama 2 i 3 za: uzrast ($p < 0,001$), F ($p < 0,001$), L ($p < 0,001$), proteinuriju ($p < 0,01$), pušenje ($p < 0,001$), HT ($p < 0,0001$), SC ($p < 0,001$), C ($p < 0,001$), LDL ($p < 0,0001$), T($p < 0,001$), muški pol ($p < 0,01$). Indeks stenoze visoko je korelirao sa sledećim faktorima rizika: uzrast, SBP, LDL-C, F, SC, proteinurija u grupi 1; sa SBP, LDC i uzrastom u grupama 2 ili 3. U bolesnika sa CHD 39,13%, je imalo ACAS, a u bolesnika sa PVD 84.37% je imalo ACAS.
Prevalenca ACAS bila je značajno viša u bolesnika sa CGN i visoko je korelirala sa faktorima rizika. Blagi i umeren stepen ACAS preovlađivao je nad teškim ACAS, i bio je značajno češći u bolesnika sa nefrotskim sindromom i hroničnom bubrežnom insuficijencijom. ACAS je često bio udružen sa CHD i PVD. Ekstrakranijalno ultrazvučno Doppler ispitivanje treba preporučiti kao rutinsko ispitivanje bolesnika sa CGN, da bi se otkrio ACAS u ranom stadijumu.

Ključne reči: *Asimptomatska stenoza karotidne arterije, faktori cerebrovaskularnog rizika, Doppler ultrasonografija, koronarna bolest srca, periferno vaskularno oboljenje*

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