THE SIGNIFICANCE OF GENETIC AND CARDIOLOGIC EXAMINATIONS IN IgA NEPHROPATHY

Ph.D theses

(Summary)

Tamás Szelestei MD

2nd Department of Internal Medicine and Nephrology Center

Medical School of the University of Pécs

Head of the Doctoral School, Head of the Ph.D progam:

Prof. Judit Nagy MD

Supervisors:

Prof. Judit Nagy MD, Tibor Kovács MD

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1. SUMMARY

The IgA nephropathy (IgAN) is the most frequent form of primary chronic glomerulonephritis worldwide. Until IgAN patients were observed for a short time, the disease was assumed to take a benign form. Long term observations showed that 20-50% of the patients need renal replacement therapy 20 years after establishing the diagnosis. It is also a characteristic feature of the IgAN patients that hypertension, which is one of the most important risk factor of cardiovascular diseases, usually develops even before the deterioration of renal function. The incidence of cardiovascular diseases is much higher in individuals with chronic renal disease that those without such a disease. However, such examinations in IgAN had not been carried out before our results were published. Even though in most cases IgAN is not hereditary, genetic factors can still play a role both in the occurrence and the progression of the illness. The variations of such genes were examined which could be assumed to play a role in the prognosis or etiopathogenesis of the IgAN.

Uteroglobin binds to fibronectin thus it can prevent the collagen-fibronectin, IgA-fibronectin interaction which leads to abnormal deposits in IgAN. Uteroglobin knock-out mice develop a renal disease very similar to IgAN. The G38A polymorphism of the uterglobin was examined and the G allele and GG genotype was significantly more frequent in patients showing progression than in IgAN patients with stabile renal function.

The mesangium cells have an important role in IgAN. Megsin is a protein with a gene only expressing in mesangium cells. According to other research data the expression of megsin in IgAN increased. Polymorphism was found in the megsin-gene (C2093T) while examining megsin, both in healthy volunteers and IgAN patients. The frequency of the C allele was 55% in the IgAN patients while it was 45.5% in their healthy controls. The difference was not significant but later Chinese researchers found that similar difference in a research with a larger number of participants is significant.

IgAN is sometimes accompanied by Crohn's disease. Autoimmunity is present in the pathomechanism of both illnesses, thus immunosupressive therapy may be effective in a number of patients, and bacterial infection can lead to exacerbation in both diseases. NOD2 is the intracellular lipopolysaccharide receptor of the monocytes, its irritation leads to inflammation. Mutations of the NOD2 gene occur more frequently in individuals with Crohn's disease than in healthy patients. Due to the common characteristics of the two

diseases, mutations of the NOD2 gene were examined in IgAN patients. Our results show that the mutations may accelerate the course of the disease.

Selectins are adhesion molecules, which could play a role in the inflammation of the kidney in IgAN. Results of an earlier Japanese study showed that the selectin polymorphisms are in a strong association with the occurrence of IgAN. Our examinations could not confirm this in Hungarian patients.

Oxidative stress also plays a role in the damages which occur. The organism protects itself from oxidative stress with antioxidant enzymes. The polymorphisms of the antioxidant enzymes catalase (CAT) and glutathione-peroxidase (GPX1) were looked at assuming that such a variation can be found with which the course of the disease is more favourable. This hypothesis could not be confirmed.

The activation of the renin-angiotensin-aldosterone system is unfavourable to the course of IgAN, with the inhibition of the angiotensin converting enzyme (ACE) the progression of the disease can be slowed down. The role of the I/D polymorphism of the ACE gene in IgAN has been studied several times but we have not found any connection neither with the occurrence nor with the progression of the disease.

One consequense of the hypertension occuring in IgAN is the development of left ventricular hypertrophy. One of the characteristic features of the hypertension in IgAN is the absence of nighttime blood pressure reduction. The connection between the absence of nighttime blood pressure reduction and the development of left ventricular hypertrophy and the occurrence of diastolic dysfunction was established even in normotensive patients. This connection was closer in hypertensive IgAN patients.

2. INTRODUCTION

The Role of Genetic Factors in IgA Nephropathy

IgAN occurs sporadically and is not considered to be hereditary. However there are some facts which suggest the role of genetic factors in the disease:

- the prevalence of IgAN shown great ethnic and geographical variation
- simultaneous development of IgAN was observed in monozygotic twins
- haematuria and proteinuria occurs more frequently in the family members of IgAN patients
- familial clustering of the disease was observed in numerous places

At the initial stages of the research there was no significant data available about the genetic background of IgAN.

Cardiovascular Diseases in IgA Nephropathy

Nearly 50% of patients with chronic nephropathy die in a cardiovascular disease before developing end–stage renal disease. However, until now the frequency and characteristics of the cardiovascular diseases have been studied only in patients with end-stage nephropathy receiving renal replacement therapy. In the beginning of the research there was no publication concerning the cardiovascular status of the IgAN patients, the article summarizing the result was the first one in the present topic.

3. HYPOTHESIS AND OBJECTIVES

3.1. Uteroglobin

Uteroglobin is one of the interesting candidate genes of IgAN because uteroglobin gene-disrupted mice developed a nephritis with pathological characteristics similar to IgAN. Deposits of IgA, collagen, fibronectin develop in the kidneys of uteroglobin gene-disrupted mice. Uteroglobin has a great affinity to fibronectin, that is, it forms uteroglobin-fibronectin heteromer thus preventing the interaction of collagen-fibronektin and IgA_1-fibronectin which is necessary for the development of abnormal deposits. Uteroglobin can also interfere with phospholipase A_2, which indirectly affects the expression of surface adhesion molecules which in turn can influence the development of the deposits. Uterglobin can also have a cytokine-like effect, as it serves as a binding protein in numerous compounds. The hypothesis of the connection between G38A polymorphism of uteroglobin and the occurrence or progression of IgAN.

3.2. Megsin

Mesangial cells play an important role in maintaining the structure and function of the glomerular cells, in forming and breaking down the extracellular matrix, and in removing the immune complexes. A Japanese research group has described a protein consisting of 380 amino acids, it is expressed only in mesangial cells, its structure (amino acid homology) suggested that it belongs to the serin-protease inhibitor (serpin) family. Hence its name megsin (mesangial cell-predominant serpin). Megsin is expressed to a greater extent in the mesangial cells of IgAN patients, than in healthy individuals or in patients suffering from other types of glomerulonephritis. In megsin transgene mice proliferation of the mesangial cells occurred and the expression of the mesangial matrix developed, which as accompanied by imunoglobuline deposition.

It was assumed that there could be a variation of the megsin gene, which is associated with the occurrence and prognosis of IgAN. The aim of the research was to find out whether the megsin gene has any common polymorphisms, and if it has any affect on the occurrence and progression of IgAN in the patients participating in the study.

3.3. NOD2

When IgAN is sometimes accompanied by Crohn's disease, it is called secondary IgAN. Crohn's disease is an inflammatory bowel disease and has several common characteristics with IgAN:

- „autoimmune-like" diseases in which steroid treatment may be effective
- they occur after bacterial infections which can also cause relapses
- they occur more frequently in men
- the beneficial effect of tonsillectomy in IgAN, and appendectomy in Crohn's disease was suggested

The association of the NOD2 genetic mutations and Crohn's disease has been described by several research groups. NOD2 (nucleotide-binding oligomerization domain 2) is expressed exclusively in monocytes, it is the intracellular receptor of lypopolysaccharide (LPS), which as a transmitter leads to the activation of the nuclear factor kappa-B (NFκB) and thus inflammation.

The activation of NFκB plays an important role in the progression of renal diseases. NOD2 could be especially interesting in IgAN because an earlier study showed that the monocytes of IgAN patients reacted with an increased cytokine production to LPS compared to the cells of healthy individuals. This suggests that IgAN patients' monocytes are different from those of healthy individuals.

In the research the following hypothesis was examined whether the NOD2 mutations occurring more frequently in Crohn's disease can also play a role in the occurrence or the progression of IgAN.

3.4. Selectin

Selectins are adhesion molecules which play a role in the interaction of endothelial cells and leukocytes, which is necessary for the leukocytes to leave the vascular system.

Earlier experiments showed that selectins can also play a role in the accumulation of leukocytes in the glomeruli and the interstitium in patients with IgAN. Examination of renal biopsies of kidney disease patients revealed an increased expression of E- and P-selectin in the extraglomerular endothelial cells. The proportion of the cells expressing L-selectin was high among the leukocytes infiltrating the glomeruli and the interstitium. The E- L- and P-selectin genes are located next to each other on chromosome 1 (1q24-q25).

There are numerous SNPs in this region which are inherited completely linked to each other (linkage disequilibrium). In a Japanese study 2 SNPs in the E-selectin (SELE) and 6 SNPs in the L-selectine revealed an association with IgAN, and the connection was found to be even stronger upon examining haplotypes made of 3 SNP.

Our hypothesis was that selectin SNPs play a role in the occurrence of IgAN in Hungarian patients, similarly to their Japanese counterparts.

3.5. Glutathione-peroxidase and Catalase

Previous experiments suggested a role of oxidative stress in the etiology and progression of IgAN.

Glutathione-peroxidases (GPX) reduce lipid and non-lipid hydroperoxides while oxidizing two molecules of glutathione. GPX-1 has only one frequent polymorphism: C593T, which leads to the exchange of the amino acid 197 proline/leucine (P197L).

In the case of severe oxidative stress catalase (CAT) has the most important function in cell protection. CAT is an enzyme present in all living things and breaks down H_2O_2 to H_2O and O_2. A C/T substitution has been described (C-262T) which influences the functioning of the promoter of the CAT. The expression of the gene is 50% greater in the case of T allele than in the case of C allele.

In a previous study of type 2 diabetic patients there was a significant connection between the GPX-1 P197L polymorphism with the serum level of methyllized arginine derivatives. There was also a significant connection with metabolic parameters such as HDL cholesterol, and a nearly significant connection with triglyceride.

The incidence of metabolic syndrome is also frequent in IgAN.

It was assumed that the polymorphisms of GPX-1 P197L and CAT C-262T can have an effect on the progression of IgAN due to the different antioxidant protection. The connection between metabolic and oxidative stress and GPX-1 P197L and CAT C-262T polymorphisms was studied.

3.6. Angiotensin-converting enzyme (ACE)

3.6.1.ACE I/D polimorphism and the progression of IgAN

The renin-angiotensin system (RAS) affects the progression of renal diseases through several mechanisms. It is an established fact that RAS inhibitors in IgAN decrease

proteinuria and slow the progression of the disease. The plasma levels of ACE can show even a five fold interindividual variation, while its level is more or less constant within one individual. The presence, insertion (I) or the absence, deletion, (D) of an Alu element in the intron 16 of the ACE gene is responsible for about 50% of the great variation in the ACE levels. In previous studies the beneficial effect of the I allele in the prognosis of IgAN was described, but other studies have not been able to confirm this.

In the present study the effect of the I/D polymorphism of the ACE gene on the progression of IgAN in Hungarian patients was studied.

3.6.2. Blood pressure and left ventricular muscle mass

A frequent consquence of high blood pressure is the development of left ventricular hypertrophy which is an independent risk factor of cardiovascular mortality. According to the data gathered with the examination carried out with the extensively used ambulatory blood pressure monitoring (ABPM) the extent of the target organ damage is in a more significant correlation with the results of a 24-hour blood pressure monitoring than the results yielded with occasional measurement of blood pressure.

In chronic GN blood pressure is often elevated even early in the course of the disease, its main feature is the absence of nighttime blood pressure reduction. Left ventricular hypertrophy and diastolic dysfunction are also frequent.

The aim of the study was to find out whether there is a relationship between the various values measured by ABPM, especially the absence of nighttime blood pressure reduction and left ventricular hypertrophy and diastolic dysfunction in patients with IgA nephropathy.

3.6.3. ACE I/D polymorphism and left ventricular muscle mass

Previous examination showed that there is no connection between the I/D polymorphism of the ACE gene and blood pressure, but in the presence of DD genotype left ventricular hypertrophy is more frequent in essential hypertension. In patients with uremia on renal replacement therapy, left ventricular hypertrophy is more frequent in the presence of DD genotype, while this relationship is not observed in patients with polycystic kidney disease.

The answer was sought to the question whether any relationship exists between ACE I/D polymorphism and left ventricular hypertrophy and other cardial parameters in IgAN patients.

4. METHODS

4.1. Patients

The 134 patients with IgAN are observed at the 2nd Department of Internal Medicine and Nephrology Center, Medical School of the University of Pécs.

The diagnosis was established through renal biopsy in every patient. History taking, physical examination, urinalysis, and creatinine clearance determination was carried out in every participant. Blood specimen was taken for DNA analysis in addition to the routine laboratory analysis. The patients received uniform treatment in the institution. An effort was made to normalize blood pressure through diet and medications in which the initial treatment almost always consisted of the administration of ACE inhibitors. The patients received immunosuppressive treatment very rarely, only in the case of severe proteinuria. Monitoring of disease progression was carried out in patients who had been followed up for at least 3 years.

Healthy volunteers were ethnically similar to the patients.

4.2. Genotyping

The sections containing the variation of the studied genes were amplified with polymerase chain reaction. Two methods for genotyping were used:

- restriction fragment length polymorphism (RFLP)
- mini-sequencing

4.3. Ambulatory Blood Pressure Monitoring (ABPM)

Patients' blood pressure was monitored with the portable Meditech ABPM blood pressure monitor, working with oscillometric principles.

4.4. Echocardiography

Almost simultaneously with the blood pressure monitoring heart ultrasound examination was also carried out with an ATL Ultramark9 HDI device. Left ventricular

muscle mass was calculated with the Penn convention: LVM=1,04[(IVS + EDD + PW)^3 - EDD^3]-13,6 g

Diastolic dysfunction was evaluated on the basis of the decrease in the mitral E wave, the increase in the A wave, and the increase in deceleration time (DT).

4.6. Statistical Analysis

The statistical analysis was carried out with the SPSS software (Statistical Package for the Social Sciences, Chicago, IL). A difference was considered to be statistically significant if $p<0.05$. In the case of normal distribution the data were given in a mean± deviation format, the difference between the groups was calculated with T-test and variance analysis. In the case of non-standard distribution the data were given in a median (minimum-maximum) format, the difference between the groups was calculated with Mann-Whitney U test.

5. RESULTS

5.1. G36A Genetic Polymorphism of Uteroglobin

GG genotype occurred in a greater proportion in patients with progressing IgAN than in patients without progression (OR 3.5; p<0,006). Also, the presence of the G allele was more frequent in patients with progression (OR 2.6; p<0,009). 1/serum creatinine over time plot was sevenfold steeper in GG patients than in the patients with AG and AA genotypes, but the difference was not statistically significant (p=0,08). The distribution of the uteroglobin genotypes and allele frequencies did not show any difference in IgAN patients and healthy individuals.

5.2. Megsin C2093T Polymorphism

There was no significant difference neither in the genotype distribution nor in the allele frequencies between IgAN patients and healthy controls, or in IgAN patients with and without progression.

5.3. G908R and 3020inC Mutations of the NOD2 Gene

During the follow up period of more than 12 years, the serum creatinine values increased by one third in IgAN patient without a NOD2 gene mutation, while the creatinine levels in the IgAN patients living with a NOD2 mutation, increased more than 4-fold.

The renal survival was examined with Kaplan-Meier analysis. A significant difference was found both when the end-point was a creatinine level of 256 μmol/l and when it was 500 μmol/l. The 256 μmol/l is considered to be the"point of no return" in IgAN by several experts.

The frequency of mutant NOD2 alleles (908R and 3020insC) was not different in patients with IgAN and healthy individuals.

5.4. Selectin Gene Polymorphisms: SELE Y468H, SELL A-642G

There was no relationship between the polymorphisms and the occurrence or the progression of IgAN.

5.5. Polymorphisms of Antioxidant Enzymes (GPX-1 and CAT)

5.5.1. GPX-1 P197L

A GPX-1 P197L polymorphism did not show any correlation neither with the development of IgAN nor with its progression.

The BMI of the PP genotype IgAN patients was lower their HDL levels were higher than those of the patients with LL and PL genotypes ($p<0.01$). The amount of AGE products and the TBARS level indicating oxidative stress level did not vary in the different genotype groups.

5.5.2. CAT C-262T

A CAT C-262T polymorphism did not show any correalation neither with the development of IgAN nor with its progression.

From among the metabolic parameter there was a significant difference concerning uric acid: in IgAN patients with CC genotypes the level of uric acid was lower that that of the CT and TT genotype patients ($p<0.05$). The amount of AGE products and the TBARS level indicating oxidative stress level did not vary in the different genotype groups.

5.6. I/D Polymorphism of the ACE Gene

5.6.1. I/D Polymorphism of the ACE Gene and the Progression of IgAN

The genotype and allele distribution of the ACE I/D polymorphism did not show any difference between patients with progressing IgAN and non-progressors.

5.6.2. Blood Pressure and Left Ventricular Muscle Mass

The result of the 24-hour monitoring

Every blood pressure parameter (systolic- diastolic; 24-hour- diurnal- nocturnal) of the IgAN patient with treated hypertension was significantly higher than those of their

normotensive counterparts. The decreased diurnal rhythm (diurnal index <10%) was frequent in both normotensive and in patients with treated hypertension.

The Results of the Echcardiographic Examinations

Left ventricular wall thickness and left ventricular muscle mass index were significantly greater in the group with treated hypertension, the E/A value was significantly lower in the group with hypertension. Left ventricular hypertrophy and diastolic dysfunction was rare among the normotensive patients, and frequent among patients with hypertension. Good systolic left ventricular function and normal cavity size was found in booth groups.

The relationship between the blood pressure parameters and the left ventricular muscle mass index and the diastolic function

There was no connection between blood pressure parameters and left ventricular muscle mass index, in normotensive patients, while the impairment in the diastolic function (which was demonstrated on the basis of both E/A and DT) correlated with nighttime systolic blood pressure and values of the diastolic diurnal index.

There was a significant correlation between left ventricular wall thickness and nighttime mean blood pressure values and diurnal index values; diastolic function had a strong connection with diastolic diurnal index values and while there was no statistic relationship with daytime and 24-hour blood pressure values.

5.6.3. I/D Polymorphism of the ACE Gene and the Left Ventricular Muscle Mass

Both the septum and the posteror wall was thicker in DD genotype IgAN patients than is II genotype patients. The results of the heterozygotes were between the results of the two homozygotic groups. The same could be observed in the left ventricular muscle mass index results which did not reach the significance level. The ejection fraction indicating systolic function was greater than DD genotype patients than in II genotypes.

6. DISCUSSION

6.1. G38A variation of the Uteroglobin Gene and IgAN

My attention was drawn to the possible role of uteroglobin that in mice with uteroglobin deficiency IgAN develops. The study of the G38A polymorphism of the uterglobin gene in IgAN was the first one. The connection was established with the progression of IgAN: GG genotype and G allele was more frequent in patients with progressing IgAN. Our result were confirmed by a larger-scale Japanese study where 239 patients were examined and the GG genotype was also found to be an unfavorable prognostic marker. Other far-eastern studies obtained different results. Thus the important role of uteroglobin in IgAN is not yet established.

6.2. C2093T variation of Megsin and IgAN

Megsin is expressed only in mesangial cells which are of paramount importance in IgAN. The function of megsin was still unknown when the increased expression of megsin in IgAN was discovered. Variations of the gene found in the NCBI internet database were tested. Such SNPs were looked for in which the frequency of the less common allele is at least 30%. The above expectation was met by the C2093T polymorphism. We were the first to research relationship of the megsin genetic variation and IgAN, but we have not found any connection between the development or with the progression of the disease. Chinese authors studied a larger number of patients and healthy volunteers, using our method. While the frequency of the C2093 allele was 55% in Hungarian IgAN patients, and 48.5% in healthy individuals, the same in Chinese IgAN patients was 70.2%, and in the healthy individuals it was 62.9%. In our examination the tendency was similar, but the difference was not significant in the Chinese study where there was a larger number of cases, the difference was statistically significant. The findings of the Chinese study was confirmed by family examinations and experiments carried out on other populations has similar results.

6.3. NOD2 and IgAN

NOD2 is the LPS receptor of monocytes which leads to NFκB activation and inflammation. Mutations of NOD2 predispose to Crohn's disease. NOD2 mutation in IgAN patients were studied due to known relatioship of IgAN and Crohn's disease and the similarities of the two diseases (bacteria, role of NFκB). In patients with NOD2 mutation the progression of IgAN was more unfavorable, but due to the low number of cases the difference was not statistically significant. According to the results, NOD2 mutations can accelerate the progression of the disease, possibly with a stronger inflammatory reaction to the same amount of LPS stimulus. Further evidence is needed in order to confirm the results.

6.4. Selectin and IgAN

Deposition of leukocytes in the glomeruli and the interstitium play a role in the development IgAN, with the selectins also participating in the process. Japanese authors have studied SNPs in the whole genome in order to examine complex diseases. The study of IgAN was carried out with the examination of the 34 SNP (SELE: 13, SELL: 15, SELP: 6) of the E, P and L selectin genes which are located next to each other on chromosome 1. The haplotype determined by 3 polymorphisms of the selectin genes showed an association with IgAN ($p=0.000016$). It was confirmed that the haplotypes have a close connection with IgAN is associated with a stronger interaction between leukocytes and endothelial cells. Our examination included 2 of the 3 SNPs in Hungarian IgAN patients and in healthy volunteers. No SNP showed any connection with IgAN. The results suggested that there may be a difference in the genetic background of the Hungarian and Japanese IgAN.

6.5. Antioxidant Enzymes (GPX-1 and CAT) and IgAN

Oxidative stress and its consequences can be demonstrated in IgAN. In response to oxidative stress the expression of antioxidant enzymes increases in IgAN. Oxidative stress plays a role in the progression of renal diseases. The detection of oxidated protein products proved to be an early prognostic marker of IgAN. The progression of chronic renal diseases can be influenced favorably by treatment with antioxidants. To this end polymorphisms of antioxidant enzymes in IgAN. were studied. Catalase and glutathione-

peroxidase polymorphisms were unrelated both to the occurrence and to the progression of IgAN.

The connection of GPX-1 and CAT genes and metabolic and oxidative stress in IgAN patients was also studied. In a previous study of type 2 diabetic patients there was a significant connection between the GPX-1 P197L polymorphism with the serum level of methyllized arginine derivatives. There was also a significant connection with metabolic parameters such as HDL cholesterol, and a nearly significant connection with triglyceride. The GPX-1 P197L polymorphism was in a significant correlation with BMI and HDL cholesterol. In the case of CAT -262T allele the gene expression is greater thus it is surprising that the CC genotype IgAN patients' uric acid level was lower.

Variations of the catalase and glutathione-peroxidase had never been studied either in IgAN or in other diseases. For this reason our results cannot be compared to those of others.

6.6. I/D polymorphism of ACE and IgAN

6.6.1. I/D Polymorphism of the ACE Gene and the Progression of IgAN

The activation of RAS can influence the progression of IgAN through several meachanisms which can be influenced favourably with the administration of RAS inhibitors. ACE I/D polymorphism in IgAN patients was studied, but no connection was found with the progression of the disease. The I/D polymorphism of the ACE gene is the most frequently studied genetic variation: several studies claim that the D allele and especially the DD genotype are negative prognostic fatcors in IgAN, while other studies did not confirm this result.

6.6.2. Blood Pressure and Left Ventricular Hypetrophy Parameters in IgAN

Blood pressure increases in parallel with the progression of chronic glomerulonephritis. Initially it increases within the normal range, and then the patients become hypertensive. There is a direct and continuous relationship between progression of hypertension and left ventricular hypertrophy independently of the etiology of hypertension. In patients with chronic glomerulonephritis the first sign of developing secondary hypertension may be the absence of nighttime blood pressure reduction. Its

pathophysiologic mechanisms, prognostic value, were not obvious at the time of the present study.

The present study reveals that the diurnal blood pressure rhythm was abnormally reduced in almost half of the normotensive patients. This in it self did not indicate antihypertensive treatment according to the treatment practice at the time, even though the value of the diastolic diurnal index was in a significant correlation with the ventricular septum thickness and the parameters of diastolic function.

The daytime blood pressure in hypertensive IgAN patients was treated in a satisfactory manner in most cases, most likely this is the reason that their blood pressure parameters did not correlate statistically either with left ventricular wall thickness, muscle mass, or with its diastolic function. ACE inhibitors though they do not change the diurnal rhythm of blood pressure, their have less effect when giving in the evening perhaps due to the lower renin level. Consequently ACE inhibitors cannot be expected to restore the diurnal rhythm which disappears so often in chronic glomerulonephritis. Accordingly, in more than half of the hypertensive patients receiving treatment the absence of nighttime blood pressure reduction persisted. Unfortunately our findings revealed that this fact is not without consequences. In hypertensive patients receiving treatment, nighttime blood pressure and the abnormal diurnal index indicating the absence of nighttime blood pressure reduction was in close connection with left ventricular wall thickness and the parameters indicating diastolic function. The findings showed that ACE inhibitor treatment indicated early in the course of the disease and normalizing daytime blood pressure does not prevent left ventricular hypertrophy and diastolic dysfunction.

Since the present examination has come to an end, several studies were published from which the following conclusion can be drawn: the results apply not only to IgAN patients but the same findings has been obtained if the cause of the azotaemia was polycystic renal disease, other glomerulonephritis, hypertension with albuminuria or type 2 diabetes, or the patient had undergone renal transplant. The conclusions have become extensively accepted. Even recommendation of the Kidney Disease Outcomes Quality Initiative (K/DOQI) about hypertension and its treatment refers to our examination as well.

6.6.3. The I/D Polymorphism of the ACE Gene and Left Ventricular Wall Thickness in IgAN Patients

The relationship between the ACE I/D polymorphism and left ventricular wall thickness in essential hypertension has been described in several studies. This connection

has been discovered in patients with uremia receiving dialysis as well but the connection has not been established in patients with polycystic kidney disease. The ACE enzyme is present in larger quantities with D allele consequently more angiotensin-II and aldosterone is produced. Both have a direct role in the development of left ventricular hypertrophy. The left ventricular wall in DD genotype IgAN patient is thicker than that of the II genotype patients. The ejection fraction of DD genotype patients is greater that that of II genotype patients. Similarly to the hyperfiltration in the kidneys, even the better systolic function is not favorable.

Recently the study of genetic polymorphisms has been subject to a great deal of criticism. A great number of factors play a role in such complicated processes as the occurrence and progression of IgA nephropathy. If we pick out one of them and begin to study that factor alone their significance often goes unnoticed. Moreover these studies do not examine direct effect just associations. This is the reason why an effort has to be made to include a large number of participants in the experiment, genetically homogenous group of patients, and the experiments should be carried out on several populations. Thus, it is not surprising that the findings of other researchers could not be confirmed, or the associations found in out study could not always be observed elsewhere.

7. THESES

I. The G38A polymorphism of uteroglobin was related to the progression of IgAN, but not with its occurrence.

II. The existence of the genetic variation of megsin C2093T was confirmed, its frequency was described in Hungarian patients. The frequency of the megsin C2093 allele in Hungarian IgAN patients is 55%, in healthy Hungarians it is 48.5%, the difference between the two groups was not statistically significant.

III. In IgAN patients with a NOD2 gene mutation the prognosis of the disease was poor.

IV. Variations of the selectin gene in Hunagrian IgAN patients were connected neither to the occurrence nor to the prognosis of the disease.

V. GPX-1 P197L and CAT C-262T SNPs were not related to the progression of IgAN, but from among the metabolic parameters they were associated with BMI, HDL cholesterol level, and uric acid.

VI. ACE I/D polymorphism was not related to the occurrence and prognosis of IgAN.

VII. Both in hypertensive and in normotensive IgAN patients the absence of nighttime blood pressure reduction is frequent, which showed a relationship with the left ventricular muscle mass and the existence of diastolic dysfunction.

VIII. In ACE DD genotype IgAN patients' left ventricular wall were thicker than in their II genotype counterparts.

8. PUBLICATIONS

Publications related to the thesis

Papers

1. **Szelestei T**, Kovács T, Barta J, Nagy J: Éjszakai hypertonia, bal kamra hypertrophia és diasztolés funkciózavar IgA nephropathias betegekben Magy BelorvArch 1998;51:23-9.
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