PhD thesis

NEW DATA ON FACTORS THAT AFFECT THE PROGRESSION OF IGA NEPHROPATHY

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1. INTRODUCTION, AIM OF THE DISSERTATION

IgA nephropathy is the most common primary form of glomerulonephritis, which has been known as Berger disease from its first description. The diagnosis of the disease can only be established after histological examination of a kidney biopsy specimen and it is, most of all, based on the deposition in the mesangial region, of the glomeruli, of IgA (mainly IgA1) demonstrated by immunohistological examination.

The precise ethiopathogenesis of the disease is not yet known, but the most widely accepted theory is that it is caused by immunocomplexes. Considering that IgA molecules play a role in the barrier function of the mucosa the role of the mucosa in the pathogenesis has been investigated ever sinc the first description of the disease.

On the basis of the frequent upper respiratory tract infections (often accompanied with macrohematuria) in IgA nephropathy and the frequency of chronic tonsillitis, observed also in our ownpatients, the role of the tonsils may be considered in the pathogenesis of the disease, and tonsilectomy might have a favourable effect on the progression of the disease by elimination of chronic antigenemia.

The occurrance of IgA nephropathy and some gastrointestinal diseases (coeliacia, ulcerative colitis, Crohn-disease) in combination raised the role of pathologic alterations of the mucous membrane of the bowel in the pathogenesis of the disease. Increased permeability of the intestinal mucosa and the provoking role of food antigens have been described in IgA nephropathy. A previous observation by our team confirmed that the level of IgA antibodies against some food antigens is higher in the serum of IgA nephropathy patients than in healthy controls.

Impaired protective capacity of the mucosa suggests, that the prevalence of urinay tract infections is higher in IgA nephropathy. These infections may play a role in the progression of the disease by damaging the tubulointerstitium.

The symptoms and course of the disease can be very variable. With the increase of follow-up time it was found that the disease, which used to be considered definitely benign is actually progressive in most patients progressing to chronic renal insufficiency in many cases, with need for renal replacement therapy 15-25 years after its onset. In wiew of the cardiovascular risk factors playing an important role in the progression of IgA nephropathy, early diagnosis and effective treatment of hypertension are the most important tasks.

The frequent progression observed in IgA nephropathy led us to carefully study the different prognostic factors. My investigations were based on results and observations about IgA nephropathy patients in the Second Department of Medicine of the University Medical School of Pécs over a period of 30 years.

The aims of my PhD thesis can be summarized as follows:

- Investigation of the role of permeability of the bowels and of food antigens in the ethiopathogenesis of the disease.
- Effect of tonsillectomy performed in the case of chronic tonsillitis during the progression of IgA nephropathy.
- Role of recurrent urinary tract infections in the progression of the disease.
- Investigation of the factors that affect the development (endothelial factors), diagnosis (24-hour blood-pressure monitoring), complications (cardiac) and therapy of hypertension in our patients in the followed-up program.

II. METHODS

1. Investigation of bowel permeability and food antigens.

The sporadic simultaneous occurrance of some inflammatory bowel disease and IgA nephropathy raised the possibility of a lesion of the mucous membrane of the bowel in the pathogenesis of IgA nephropathy, so we investigated the permeability of the bowel in IgA nephropathy patients with 51Cr-EDTA. Because food antigens can easily pass though the increasingly permeable mucous membrane of the bowel causing a chronic antigen stimulus, we investigated the level of eight antibodies against antigens, of partly floral and partly animal origin in the serum of patients.

2. Tonsillectomy

IgA nephropathy often presents or recurs with recurrent macroscopic hematuria, often accompanied by upper respiratory tract infections or tonsillitis. Tonsillitis is very frequent in IgA nephropathy patients, so we followed the progression of the disease after tonsillectomy in our followed-up patients.

3. Recurrent urinary tract infections

As a result of reduced capacity of the mucous membrane, urinary tract infections with or without symptoms can also cause tubulointerstitial damage and increased progression of

IgA nephropathy. The urine of the patients was regularly tested microbiologically at every check inspection.

4. Hypertension

a./ Endothelial vasoactive agents

In the last few years the role played by numerous endothelial vasoactive mediators in the physiological and pathophysiological function of the kidney has been investigated. Among these mediators we investigated nitrogen monoxide (NO) and endothelin (ET), because both NO and endothelin (in addition to local vasoregulation), take part in the mediation of inflammatory processes in the kidney. The level of excreted NO_2^-/NO_3^- (NOx) - as stable endproduct of NO - and that of endothelin were investigated in 24-hour samples of urine collected from IgA nephropathy patients. Considering that the factors that affect the measurement of NOx in the urine were not known, we first standardized the method for collecting urine. During the investigation of endothelial cell cultures in our previous studies we found that cigarette smoke decreased NO production of the cells. Therefore we also investigated the connection between smoking and NOx excretion in IgA nephropathy patients and compared it with controls.

b./ Ambulatory blood-pressure monitoring

The connection between hypertension and the progression of chronic renal diseases has been well known for a long time. This is why early diagnosis and effective treatment of hypertension is of special importance in chronic glomerulonephritis, thus in IgA nephropathy.

We have employed 24-hour ambulatory blood-pressure monitoring in large numbers of our IgA nephropathy patients. When analysing the results we made numerous observations.

c./ Echocardiography

The absence of decrease in nocturnal blood-pressure (non-dipper) is very common before the development of hypertension in IgA nephropathy, which may be of prognostic importance or possibly have an end-organ-damaging effect. Diurnal blood pressure was normalized by antihypertensive treatment (ACEI±CCB), which however did not restore the diurnal rythm. On the basis of this, we prformed echocardiography in IgA nephropathy patients and we analyzed the results together with the data of ABPM.

d./ Therapy

To compare the renoprotective effect of short and long acting ACE inhibitors and CCB-s, the renoprotective effect of short acting (administered 3 or more times a day) and the long acting (administered once or twice a day) antihypertensives were compared with each other.

III. NEW RESULTS AND CONCLUSIONS

Investigation of permeability of the bowels and food antigens

I. In IgA nephropathy the permeability of the bowels is and remains increased for a long time.

II. In patients with increased permeability of the bowels and the deterioration of renal function is faster.

III. A direct correlation exists between permeability of the bowels and the titer of some antibodies against some food antigens and the pathologically increased serum IgA levels.

Tonsillectomy.

IV. Six months after tonsillectomy the severity of proteinuria and hematuria decreased significantly, but this did not prevent slow progression of the renal diasease.

Recurrent urinary tract infections.

V. In a considerable proportion of patients (25%) significant bacteriuria without symptoms can be observed. Most of these cases cause no symptoms.

VI. In IgA nephropathy patients with significant bacteriuria - treated with antibiotics - the progression of the renal disease is not increased.

Hypertension

a./ Endothelial vasoactive mediators.

VII. Depending on the number of germs the level of urinary NOx is influenced by bacterial contamination of the urine.

VIII: On the basis of the connection observed between NOx excreted in the urine and the average blood-pressure values of 24-hour ambulatory blood-pressure monitoring, NO may play a role in the regulation of hypertension.

IX. A considerable amount of NO/NOx enters the body during smoking, therefore the examination of urinary NOx can not be used to estimate NO production.

b./ Ambulatory blood-pressure monitoring

X. On the basis of ambulatory blood-pressure monitoring the occurrence of the white-coat effect is similar to that in the average population. The deterioration of renal function in non-dipper patients and normotensive IgA nephropathy patients with white-coat effect is faster.

c./ Echocardiography.

XI. Even in normotensive IgA nephropathy patients a disturbance of diastolic function develops for which the absence of nocturnal decrease in blood-pressure may be responsible.

XII. ACE inhibitors can not prevent the development of left ventricular hypertrophy in IgA nephropathy patients.

d./ Therapy

XIII. The progression of IgA nephropathy in cases of hypertension can better be reduced by treatment based on result of the 24-hour blood-pressure monitoring and by the administration of long-acting ACE inhibitors +/- CCBs.

On the basis of my investigations increased permeability of the bowels, which has persisted for a long time, may play a role in the pathogenesis of IgA nephropathy. Because of this foods which act as antigens, can constantly enter the body. This fact may play a role in the development of the high IgA antibody titers produced against the various food-antigens found in our experiments. After removal of the tonsils, acting as focus, an improvement of the clinical signs and symptoms was observed, however tonsillectomy did not prevent slow deterioration of renal function. According to our data recurrent urinary tract infections due to

the decreased defence capacity of the mucous membranes, without or with moderate symptoms, which was observed in 25% of our patients, may play a role in the progression of IgA nephropathy. In addition to the factors well known from the literature, we demonstrated that bacterial infection of the urine also changes its NO level. The connection between urinary NOx and cGMP excretion supports our hypothesis, that both of them were produced by the influence or degradation of NO. The significant correlation between NOx excretion and 24-hour blood-pressure values proves the effect of NO on blood-pressure regulation. According to our data, with increasing age, the urinary NOx level (NO production of the body) decreases. On the basis of the significantly increased NOx excretion observed in smokers and the absence of a correlation between urinary NOx and cGMP, we assume that large amounts of NO or NOx enter the body during smoking. ABPM is indispensable for early recognition and effective treatment of hypertension in IgA nephropathy. According to our follow-up data, the progression of renal disease is faster not only in hypertensive IgA nephropathy patients, but also in non-dippers and patients with white-coat effect. According to our observations, the correlation between the disturbance of diastolic function and increased nocturnal blood-pressure can be observed even in normotensive IgA nephreopathy patients. The left ventricular hypertrophy developing in spite of satisfactory blood-pressure control and cardioprotective ACE inhibitor treatment is probably related to the nocturnal hypertension occuring after cessation of the diurnal fluctuations in blood-pressure and can not as yet be satisfactorily influenced. The progression of IgA nephropathy was slower with long-acting antihypertensives (administered once or twice a day) which was probably due to a better blood-pressure profile, the more pronounced effect on decreasing proteinuria and better compliance of the patients.

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