Kidney crisis in systemic sclerosis

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Abstract

Renal crisis in systemic sclerosis occurs in the group of patients with rapid and aggressive course of the disease, often after several years of the ailment and with the diffuse form. Scleroderma renal crisis (SRC) is most frequently characterized by malignant hypertension, renal insufficiency, and less often by the symptoms of microangiopathic hemolytic anemia. Renal crisis symptoms appear suddenly and are not usually preceded by significant prodromal symptoms. SRC is always life-threatening and requires specific treatment with drugs blocking angiotensin-converting enzyme. Early diagnosis and introducing appropriate treatment give a patient a chance to survive SRC episode and improve his prognosis. SRC is of great importance to clinicians as it still causes high mortality rate.

Chronic and subacute renal crisis is connected with a small risk of acute renal failure. However, it gradually leads to a substantial dysfunction of this organ. Thus, a useful examination in the diagnostics of chronic renal crisis is checking the vascular flow in renal cortex and evaluating intrarenal resistance.

Key words: kidney, scleroderma renal crisis, systemic sclerosis.

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Introduction

Systemic sclerosis is the connective tissue systemic disease of unknown etiology and multiorgan localization. It is characterized by immunological disorders, inflammatory damage of vascular endothelium, skin fibrosis and hardening, and internal organ functioning impairment. The skin, the osteoarticular system, cardiovascular system, respiratory system, the digestive tract, kidneys, and the nervous system are the tissues and organs most frequently affected in the course of the disease. Internal organs are usually influenced in the first years of the disease and the localization of the changes and their intensity have the impact on the course and prognosis of the disease.

The kidneys affected in the course of the systemic sclerosis were reported for the first time in 1863 [1]. During the next century, numerous observations concerning the disease proved the mortality of patients with the systemic sclerosis with nephropathic symptoms to be significantly higher comparing patients without kidney failure. In 1952, Moore and Sheehan claimed the renal damage to be the main cause of death of patients with the systemic sclerosis and presented the first description of the so-called scleroderma renal crisis (SRC) [1]. Introducing drugs blocking angiotensin-converting enzyme (ACE) was the turning-point in the history of diagnostics and therapy of patients with the systemic sclerosis [2]. During 20 years of observation of patients treated with ACE inhibitors it was stated that the rate of SCR episodes diminished.

Sudden renal episodes are not the only problem of rheumatologists and nephrologists. Patients with systemic sclerosis are exposed to chronic and progressive renal damage, which can lead to renal failure. So far, the pathogenesis of renal changes in systemic sclerosis, both acute and chronic, has not been known. The study concerns the pathogenesis, clinical symptoms, laboratory tests, therapy, and distant effects of SRC in patients with systemic sclerosis.

Pathogenesis

The primary site of kidney damage is the internal membrane of a blood vessel where thinning and proliferation and, at the later stages, vessel occlusion occur. The process concerns mainly intralobular and arched vessels, i.e. renal cortex. It is assumed that an unknown etiological factor leads to endothelial damage and blood platelets appear as the first at the site of damage. Then, inflammatory cells (lymphocytes and macrophages) stimulate, producing proinflammatory cytokines, inflow of other cells, typical for inflammation. Selectins (V-CAM, I-CAM) and adhesins, proinflammatory factors secreted by the vascular epithelium, have also a great impact [3].

A trigger factor – an inflammatory process initiator – is not certain. Cannon has observed that the vascular spasm in a mechanism resembling Raynaud's symptom occurs in 75% of patients with SRC and leads to a significant decrease in renal blood flow [4]. Kovalchik et al. showed that hyperreninemia occurs in patients with systemic sclerosis without affecting the kidneys always after exposition to cold. However, during a 10-year prospective observation of 57 patients with systemic sclerosis and elevated renin concentration, none of the patients complained of the acute renal episode [5]. The vessel damage is a phenomenon, which is always present in patients with systemic sclerosis but does not coexist with SRC. In post mortem examinations, vascular endothelial damage in cases of systemic sclerosis with developed SRC was comparable to the cases without SRC.

SRC – clinical and laboratory symptoms. Definition and occurrence rate

SRC is defined as a newly ensuing malignant arterial hypertension and/or rapidly progressing renal failure with oliguria in patients with systemic sclerosis. Benign arterial hypertension in patients suffering from systemic sclerosis with elevated parameters of renal efficiency is not described as SRC [6].

The occurrence rate is estimated to be 10% of all systemic sclerosis cases. A higher risk of renal crisis can be found in patients with diffuse systemic sclerosis and reaches 20-25% in this group of patients [7]. Out of all SRC episodes, 75% occurs in the early stage of the disease, i.e. in the first 4 years after the diagnosis [8]. The symptoms are found significantly more frequently in men and the black race [9]. Predisposing factors are: the black race, the diffuse form of systemic sclerosis, rapidly occurring process of skin thinning, the disease duration up to 4 years, anti-RNA polymerase III antibodies [10], symptoms of new anemia without a clear cause, proteinuria >250 mg/d, new cardiac episodes (pericarditis, circulatory failure), and large doses of corticosteroids [11]. Other factors, also inducing symptoms, leading to SRC can be: pregnancy (hormonal changes) [12], sepsis, any clinical situation leading to dehydration (decrease in renal blood flow), any situation in the organism which causes contraction of arterioles supplying periglomerular apparatus and drugs (e.g. Ca-blockers – decrease in renal blood flow), non-steroid anti-inflammatory drugs (prostaglandin production decrease, lack of their vasodilative function), and small doses of steroids [13]. As far as the last group is concerned, there is no proof of their causative functions in development of SRC; some authors even used them to treat the disease. However, as they inhibit prostacycline production, they can have undesirable effect.

On the other hand, such factors as earlier history of hypertension, abnormal results of urine sediments, elevated creatinine concentration in blood serum, increased renin activity in blood serum, pathological picture/image of renal vessels, and antibodies SCL-70 and ACA do not influence SRC occurrence rate.

Clinical symptoms of SRC

The clinical symptoms of scleroderma renal crisis are not characteristic, specifically in its early stage. These are: fatigue, effort-rest dyspnoea, and headaches. On subjective examination, growing hypertension (which exceeds 150/90 mmHg in 90% of patients while in 30% diastolic pressure is more than 120 mmHg) seems to be important. It should be also taken into consideration that in the early stage of the disease, 50% of patients do not reveal full SRC clinical symptoms and 10% with SRC have normal blood pressure [14]. There are also clinical symptoms that are rare but specific. These are: rapidly growing hyperazotemia with no apparent cause, microangiopathic hemolytic anemia, pulmonary hemorrhage, thrombocytopenia, and neurological disorders. The presence of the symptoms requires careful observation and determination of SRC occurrence.

Cardiologic symptoms are decisive as for survival of a patient with acute renal episode. They are usually conditioned by kidneys status and blood pressure and disappear after the pressure compensation. Most severe and frequent symptoms are circulatory insufficiency, pulmonary edema, pericardial and peritoneal exudates [15].

There are laboratory tests useful in the diagnostics of acute renal episodes:

1. Renal parameters:
   - proteinuria (up to 2.5 g/24 hours)
   - erythrocyturia
   - hyaline casts in sediment
   - growing creatinine concentration in blood serum (0.5--1.0 mg/dl/24 hours) – regardless hypotensive therapy introduction
   - elevation of renin activity of blood plasma;
2. Hematologic parameters:
   - microangiopathic hemolytic anemia – normochromic anemia with fragmented red blood cells, elevated reticulocytic values and thrombocytopenia.

Other forms of affected kidneys in systemic sclerosis

Besides the acute form of SRC, there are two others, which can occur in the course of systemic sclerosis: subacute and chronic ones. The chronic SRC is asymptomatic and is characterized by a slight proteinuria, renal filtration lowering, and elevated resistance indices/coefficients in renal vessels. This form is relatively frequent, according to some investigators it can occur in 40-50% of all patients with systemic sclerosis [16].

The subacute form, with occurrence rate of 10-25%, is characterized by overt proteinuria, hypertension or normotension, and creatinine clearance decrease. Hypertension, proteinuria, and hyperazotemia can be also present. However, the course is mostly asymptomatic. The clinical picture can be disturbed by immunomodulating therapy (D-penicylamine, which causes proteinuria due to membranous glomerulonephritis). Coexisting diseases of the genitourinary system may often intensify renal changes. The diagnostics based on kidney Doppler analysis, and specifically the evaluation of intravascular resistance in the renal cortex enables precise differentiation of the clinical conditions mentioned above.

SRC treatment

In 1970s, ACE-I was used to treat SRC for the first time. A so-called blockade of the erroneous path was administered by Lopez-Ovejero in Pittsburgh in 1979 [2]. The effects of the therapy were surprisingly high, not mentioning their influence on the prophylaxis of renal complications. After ACE-I treatment 55% of patients with SRC revealed renal parameter and blood pressure normalization. Unfortunately, 15% of patients die despite introducing the therapy. According to Whitman, a significant factor limiting ACE-I application is creatinine concentration in blood serum exceeding 4 mg% [17]. In such cases, isolated ACE-I treatment did not show any improvement. Dialysotherapy proved to be successful in patients with SRC and its combination with ACE-I should be conducted for 6-12 months to avoid hyperreninemia and hyperazotemia recurrences. Blood pressure should be maintained at the level of 120-140/70-90 mmHg and ACE-I doses modified every 6-12 hours dependent on the pressure. If blood pressure values are not lowered using ACE-I treatment Ca-blockers, hydralazine, minoxidil, and sodium nitroprusside can be added [18].

Prognosis

At present, 76% of patients with SRC live for one year comparing 15% in the past. SRC prognosis is similar to that of diffuse systemic sclerosis. There is no doubt that ACE blockers have been the turning point in systemic sclerosis therapy, renal therapy and prophylaxis [19].

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