Renal Involvement in 25 Patients with Systemic Sclerosis

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ABSTRACT:

BACKGROUND:

Renal involvement is considered a poor prognostic factor and not frequently a cause of death in patients with scleroderma. Renal involvement can be divided into scleroderma renal crisis and non-renal crisis abnormalities.

OBJECTIVE:

To evaluate the frequency of renal involvement in 25 Iraqi patients with systemic sclerosis (SSc).

METHODS:

Twenty five patients with SSc (21 female and 4 male) were included in a case-controlled study. All patients fulfilled the American College of Rheumatology criteria for SSc. All patients were of diffuse type. Other types of SSc were excluded. All patients underwent measurement of blood pressure and investigations had been done for them which included: hemoglobin (Hb), white blood cell (WBC) count, platelet count, erythrocyte sedimentation rate (ESR), blood urea (BU), serum creatinine (SCr), general urine examination (GUE), and rheumatoid factor (RF). Same investigations were done for 25 healthy person (considered as control group).

RESULT:

All patients (100%) had Raynaud's phenomenon, 23 patients (29%) had dysphagia, 21 patients (84%) had arthralgia, 10 patients (40%) had telangiectasia and 2 patients (8%) had subcutaneous calcification. Three patients (12%) had moderate hypertension. Fourteen patients (56%) had anemia, 2 patients (8%) had leukocytosis, 6 patients (24%) had elevated ESR, 1 patient (4%) had elevated BU, 1 patient (4%) had albuminuria and 4 patients (16%) had positive RF. Platelet count and SCr were normal in all patients. Only 1 patient (4%) had renal involvement in form of combination of azotemia, albuminuria and hypertension.

CONCLUSION:

Renal involvement in systemic sclerosis among Iraqi patients is rare.

KEY WORDS: renal, iraqi, systemic sclerosis.

INTRODUCTION:

Systemic sclerosis (SSc)

Systemic sclerosis is a chronic, multisystem disease of unknown etiology characterized by autoimmunity and inflammation, functional structural abnormalities in small blood vessels, and progressive fibrosis of the skin and visceral organs[1].

Systemic sclerosis is a rare, acquired, non-contagious disease[2]. Its incidence is between 2.6 and 20-28 per million per year. The overall female;male ratio was reported as 3:1[3-6]. The average onset of SSc occurs between 40 and 50 years[7].

Clinically, SSc may be divided into different subtypes: diffuse scleroderma, limited scleroderma, scleroderma sine scleroderma, overlap syndrome, undifferentiated connective tissue disease and localized scleroderma which includes morphea and linear scleroderma[8].

Systemic sclerosis characterized by involvement of extremities, skin, gastrointestinal tract, lungs, heart, joints and tendons, muscles, and renal system[8].

Renal involvement in scleroderma

Renal involvement in scleroderma is considered a poor prognostic factor, and not frequently a cause of death in patients with scleroderma[9].

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Classification

Renal involvement can be divided into: scleroderma renal cisis (SRC)[10-11] and non-renal crisis abnormalities in form of hypertension, azotemia and proteinuria[12].

Scleroderma renal crisis, the most common cause of death in SSc prior to the introduction of angiotensin-converting enzyme (ACE) inhibitors, remains an important source of patient morbidity in SSc[13]. Scleroderma renal crisis is of two types: typical type and normotensive type. Moore and Sheehan in 1952 first described SRC, which is characterized by renal insufficiency (serum creatinine more than or equal to 2.0 mg/dl or a doubling of serum creatinine above the value at baseline, in the absence of another defined cause) and malignant hypertension (systolic blood pressure more than or equal to 160 mmHg or diastolic blood pressure equal to or more than 110 mmHg on at least two occasions, a minimum of 12 hours apart), accompanied by persistent urinary abnormalities or evidence of microangiopathic hemolytic anemia which often occurs in diffuse cutaneous scleroderma[10].

Normotensive renal cisis, characterized by a slow rise in creatinine in the absence of significant blood pressure elevation and without a microangiopathic picture, also has been described in SSc[14]. It is generally accompanied by anti-neutrophil cytoplasmic antibody (ANCA)-positive crescentric glomerulonephritis, and it often occurs in limited cutaneous scleroderma[11].

Epidemiology

Scleroderma renal cisis occurs in approximately 10% of all scleroderma patients. Patients with diffuse scleroderma are at greatest risk, with up to 20 to 25% of these patients developing SRC[15]. Scleroderma renal cisis is most often encountered early in the course of the disease, with 75% of cases occurring within four years after the first symptom attributable to scleroderma. Scleroderma renal crisis occurs more commonly in black patients, and male are affected more frequently than female[16].

Pathogenesis

Narrowing of the lumen of renal arterioles, leading to decreased blood flow. Elevated rennin level stimulates further vasoconstriction through increased angiotensin level; thus, a cycle is established that resulted in elevation of arterial pressure to malignant levels. The result was rapid progression to end-stage renal disease, often with concomitant cerebrovascular accidents and/or heart failure[17].

Clinical features and investigations

Manifestations of SRC are malignant hypertension, hypernatremia, hyperreninemia, azotemia, microangiopathic hemolytic anemia and renal failure[15]. Complications of renal crisis include hematuria, and proteinuria[16]. Scleroderma renal crisis occurs in 25% of patients with RNA polymerase III antibodies, also occurs in patients with anti-topoisomerase antibodies. Unlike typical SRC, ANCA-related rapid deterioration of renal function has no sign of malignant hypertension, hypertensive retinopathy or hyperreninemia in most cases, and it shows various types of autoantibodies (anti-DNA, anti-Scl-70 and anti-nRNP antibodies), mostly occur later in the disease[18].

Treatment

Scleroderma renal crisis and renal failure were the leading cause of death in SSc until the advent of effective therapy[16]. The outcome of SSc has improved dramatically with the use of angiotensin converting enzyme (ACE) inhibitors[16]. Treatment of another type of renal involvement in scleroderma patients (ANCA-related) may involve steroid therapy and/or other immunosuppressive agents (e.g. cyclophsphamide) and plasmaphoresis[11].

AIM OF STUDY:

To evaluate the frequency of renal involvement in Iraqi patients with progressive systemic sclerosis.

PATIENTS AND METHODS:

PATIENTS:

This study is a case-controlled study. Twenty-five patients attending Rheumatology Clinic in Baghdad Teaching Hospital from December 2006 to June 2007 were included in the study. All patients had fulfilled the American College of Rheumatology (ACR) criteria for SSC[19]. Patients included were all of diffuse type of SSC. Other types of SSc were excluded.

Another 25 healthy individuals matched for age- and sex with patients were studied and served as a control group.

METHODS:

Clinical assessment was done with a comprehensive protocol. Full history was taken from each patient including name, age, sex, address, clinical features, duration (duration of disease from the onset of signs and symptoms of SSc till the time of admission to the

study) and treatment. All patients were evaluated for Raynaud's phenomenon, dysphagia, arthralgia, skin thickening and subcutaneous calcification. Blood pressure was examined for all patients at least two times with one hour interval between them. In order to differentiate between normal and abnormal readings of BP, we depend on WHO classification of hypertension[20].

All patients were sent for investigations which include: hemoglobin(Hb), white blood cell (WBC) count, platelet count, erythrocyte sedimentation rate (ESR), general urine examination (GUE), blood urea (BU), serum creatinine (SCr) and rheumatoid factor (RF).

Statistical analysis

All data were arranged and tabulated in number and percentage (%). EP16 computer software program were used to measure the association between different variables by Chi-square and Fisher's test. P-value less than or equal to 0.05 is considered as significant.

Results:

A total of 50 persons (25 patients and 25 controls) were included in the study. The patients' age were ranged between 22-58 years, the mean age was 41.36 +/- 8.88 years. A female:male ratio of 5:1. the disease duration was ranging between 1-20 years. Table (1) shows the distribution of studied sample according to age and gender.

Raynaud's phenomenon was the most common symptom, which was seen in 25 patients (100%), followed by dysphagia which was reported in 23 patients (92%) and arthralgia in 21 patients (84%). Clinical features of patients with SSc including in the study are shown in Table (2).

Twenty-two patients (88%) were on penicillamine, and 3 patients (12%) took methotrexate as disease modifying drugs. Three patients (12%) on ACE inhibitor (captopril)as treatment of hypertension. Another three patients (12%) on vasodilator drug (nifidipine) as treatment of Raynaud's phenomenon.

In this study, 3 patients (12%) had moderate hypertension, 14 patients (56%) had abnormal low values of Hb (normal value of Hb in male is 13.5-17.5 g/dl and in female is 12-16 g/dl), 2 patients (8%) had leukocytosis (normal WBC count is 4000-11000 cell/mm^3), 6 patients (24%) had abnormal elevated ESR (normal value in male is 0-15 mm/hour and in female is 0-20 mm/hour), 1 patient (4%) had mild elevation of BU (normal value is 20-40 mg/dl), 1 patient (4%) had albuminuria, 4 patients (16%) had urinary tract infection, and 4 patients (16%) had positive RF. Platelet count and SCr were normal in all patients.

In control group, 1 person (4%) had mild hypertension, 4 persons (16%) had abnormal low values of Hb, 2 persons (8%) had urinary tract infection, and 1 person had positive RF. White blood cell count, ESR, platelet count, BU and SCr were normal in all persons. For all parameters mentioned above, the differences between patients and controls were statistically not significant except for anemia and elevated ESR (p = 0.0032 and p = 0.01 respectively), Table (3).

Table (1): The age and sex distribution of patients with systemic sclerosis group and control group.

	Patients (no. = 25)	Controls (no. = 25)	p-value
Age, years (mean +/- SD)	41.36 +/- 8.88	40.36 +/- 9.28	0.69 NS
Gender, no. (%) Female Male	 21 (84%) 4 (16%)	 20 (80%) 5 (20%)	 0.5 NS

NS = not significant

Table (2): Clinical features of patients with systemic sclerosis included in the study.

Clinical features	NO.	(%)*
Raynaud's phenomenon	25	100
Dysphagia	23	92
Arthralgia	21	84
Telangiectasia	10	40
Subcutaneous calcification	2	8

* Same patient might have more than one clinical feature.

Table (3): Distribution of studied samples (patients with systemic sclerosis & controls) according to clinical findings and laboratory investigations.

Clinical finding & laboratory investigation	Patients, no. (%)	Controls no. (%)	p-value
Blood pressure - Normal - Elevated	 22 (88) 3 (12)	 24 (69) 1 (31)	0.3 NS
Hemoglobin - Normal - Low	 11 (44) 14 (56)	 21 (84) 4 (16)	0.0032 S
White blood cell - Normal - Elevated	 23 (92) 2 (8)	 25 (100) 0	0.23 NS
Erythrocyte sedimentation rate - Normal - Elevated	 19 (76) 6 (24)	 25 (100) 0	0.01 S
Blood urea -Normal - Elevated	 24 (96) 1 (4)	 25 (100) 0	0.5 NS
General urine examination - Normal - Abnormal	 20 (80) 5 (20)	 23 (92) 2 (8)	0.4 NS
Rheumatoid factor - Negative - Positive	 21 (84) 4 (16)	 24 (96) 1 (4)	0.17 NS

NS = not significant S = significant

DISCUSSION:

Although SSc is believed to be a rare disease in comparison to other collagen disease in rheumatology practice in Iraq, yet we were able to collect 25 patients attended Baghdad Teaching Hospital in 6 months period.

In this study, the patients' age were ranging between 22-58 years, with a peak in the 3rd and 4th decades. This finding is different from that from study done by Cassidy et al[21], which showed a peak in the 4th and 5th decades of life. The same result was obtained by Abdulla et al[22] in a study done in Iraq in 1992.

In our study, female represents 84% of the patient, and female:male ratio was 5:1. In another study[22], it was 8.5:1.

Table (4) shows a comparison between this study and study done by Abdulla et al regarding clinical features. Raynaud's phenomenon was the most common symptom in our study. The same result was obtained by the above mentioned study[22].

In our study, 3 patients (12%) were hypertensive (hypertension was moderate in severity). In control group, there was only 1 person (4%) with mild hypertension, which was discovered accidantly. The difference was statistically not significant. This finding was comparable to that recorded in a study done by Gupta et al[23], which was 12.6%; and higher than that obtained by Abdulla et al study[22], which was 4%.

In this study, 14 patients (56%) were anemic, while only 4 persons had low level of Hb in control group. The difference between patients and control groups was statistically significant (p = 0.0032). this finding is higher than that obtained from Abdulla et al study[22], in which only 30% of patients were anemic. This anemia may be due to dysphagia and chronicity of disease[24], and the difference between two studies may be attributed to the fact that our patients have longer duration of the disease.

Two patients (8%) were having leukocytosis in our study, and all controls had normal WBC count. The same result was obtained by Abdulla et al study. Slight elevation of WBC count in patients with SSc

was reported in a study done by Leroy[25].

Six patients (24%) showed ESR elevation, and all controls had normal ESR. This result was different when compared to another study[22], in which 76% of patients have ESR elevation. This difference may be due to difference in disease activity between patients in studies. The ESR elevation may represent disease activity or superadded infection[24].

One patient (4%) showed elevation in BU. When compared to another study[22], BU was elevated in 9% of patients. The same patient had albuminuria (24-hour urinary protein was 550 mg. Renal biopsy was not done because of the refusal of the patient. Four patients (16%) had urinary tract infection proved by urine culture. All controls had normal urinalysis except 2 persons (8%) had urinary tract infection. These results were comparable to that obtained by previous authors[22, 23].

Four patients (16%), and 1 person (4%) in control group had positive RF (the difference was statistically not significant). When compared to our study, positive RF is more common in patients studied by Abdulla et al and Steen[22, 26].

Applying the criteria of renal involvement (azotemia, proteinuria and hypertension), only 1 patient (4%) had renal involvement related to SSc, which was of non-renal crisis type. This result was comparable to that obtained by previous study done in Iraq[22], in which 4.9% of patients had non-renal crisis; and it was much lower than result obtained by Steen et al[15], in which non-renal crisis reported in 25% in diffuse-type of SSc. This may be due to less severity of disease in our population.

CONCLUSION:

Renal involvement in progressive systemic sclerosis is rare among Iraqi patients.

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