

# Left renal atrophy in sickle cell diseases

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## Abstract

**Background:** We tried to understand whether or not there is a difference in occurrence of renal atrophy between the left and right sides in sickle cell diseases (SCDs).

**Methods:** All patients with SCDs were enrolled into the study.

**Results:** The study included 311 patients (153 females). There were seven cases (2.2%) with left renal atrophy against one case (0.3%) with right renal atrophy ( $p<0.001$ ). Associated thalassemias were detected in 44.0% and splenomegaly in 12.5% of the patients. There was digital clubbing in 6.4%, chronic obstructive pulmonary disease in 4.8%, leg ulcers in 12.8%, stroke in 7.0%, chronic renal disease in 8.6%, pulmonary hypertension in 11.8%, cirrhosis in 3.5%, coronary heart disease in 8.0%, and exitus in 5.7% of the patients.

**Conclusion:** Renal atrophy is significantly higher on the left side in SCDs. Splenomegaly induced flow disorders in left renal vessels, structural anomalies of the left renal vein including nutcracker syndrome and passage behind the aorta, and possibly the higher arterial pressure of left kidney due to the shorter distance to heart as an underlying cause of endothelial damage induced atherosclerosis, may be some of the possible causes. Because of the higher prevalences of left varicocele probably due to drainage of left testicular vein into the left renal vein, high prevalences of associated thalassemias with SCDs as a cause of splenomegaly, and tissue ischemia and infarctions induced edematous splenomegaly in early lives of the SCDs cases, splenomegaly induced flow disorders of left renal vein may be the most significant cause among them.

**Key words:** Sickle cell diseases, splenomegaly, left renal vein, left renal atrophy

## Introduction

Arterio- or atherosclerosis, but not venosclerosis, is an inflammatory process, probably developing secondary to the much higher arterial pressure induced chronic endothelial damage all over the body. It may be the main cause of aging induced end-organ failures in human beings (1,2). It is a systemic and irreversible process initiating at birth, and accelerated by many factors. The accelerating factors known for the moment are collected under the heading of metabolic syndrome. Some reversible components of the syndrome are overweight, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, white coat hypertension, impaired fasting glucose, impaired glucose tolerance, and smoking for the development of terminal consequences such as obesity, diabetes mellitus (DM), hypertension (HT), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), peripheral artery disease (PAD), stroke, and other end-organ failures (3-8). Sickle cell diseases (SCDs) are a prototype of the accelerated atherosclerosis (9,10), by which we can observe terminal consequences of the metabolic syndrome very early in life. SCDs are caused by homozygous inheritance of the hemoglobin S (Hb S). Hb S causes erythrocytes to change their normal elastic structures to hard bodies. Actually, rigidity instead of shapes of the erythrocytes is the central pathology of the SCDs. The rigidity process is probably present in whole life, but exaggerated with stresses. The erythrocytes can take their normal elastic structures after normalization of the stresses, but after repeated attacks of rigidity, they become hard bodies, permanently. The rigid cells induced chronic endothelial damage causes tissue ischemia, infarctions, and end-organ failures even in the absence of obvious vascular occlusions due to the damaged and edematous endothelium. We tried to understand whether or not there is a difference according to the renal atrophy between the left and right sides in the SCDs patients.

## Materials and Methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and May 2013. All patients with SCDs were enrolled into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC) method. Their medical histories including smoking habit, regular alcohol consumption, leg ulcers, and stroke were learnt. Cases with a history of three pack-year were accepted as smokers and cases with a history of regular alcohol consumption with one drink a day for three years were accepted as alcoholics. A check up procedure including serum iron, total iron binding capacity, serum ferritin, serum creatinine value on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an electrocardiogram, a Doppler echocardiogram, an abdominal ultrasonography, and a computed tomography of the brain were performed. Cases with acute painful crisis or any other inflammatory event were treated at

first, and then the spirometric pulmonary function tests to diagnose COPD, the Doppler echocardiography to measure the systolic pressure of pulmonary artery, renal and hepatic function tests, and measurement of serum ferritin level were performed on the silent phase. Renal atrophies were detected ultrasonographically. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (11). Systolic pressure of the pulmonary artery of 40 mmHg or higher during the silent phase is accepted as pulmonary hypertension (12). CRD is diagnosed with a permanently elevated serum creatinine level of 1.3 mg/dL or higher on the silent phase. Cases with renal transplantation were put into the CRD group. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, ascites, and histologic procedure in case of requirement. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of higher than 1.0 and with the presence of Schamroth's sign (13,14). Associated thalassemias are diagnosed by serum iron, total iron binding capacity, serum ferritin, and the hemoglobin electrophoresis performed via HPLC method. A stress electrocardiography was performed in cases with an abnormal electrocardiogram and/or angina pectoris. A coronary angiography was obtained just for the stress electrocardiography positive cases. So CHD was diagnosed either with the Doppler echocardiographic findings as the movement disorders of the cardiac walls or angiographically. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 311 patients with the SCDs (153 females and 158 males). The mean ages of them were  $28.2 \pm 9.2$  (8-59) versus  $29.9 \pm 9.6$  (6-58) years in females and males, respectively ( $p > 0.05$ ). Interestingly, there were seven cases (2.2%) of the left renal atrophy against only one case (0.3%) of the right renal atrophy ( $p < 0.001$ ) among the study cases (Table 1). On the other hand, associated thalassemias were detected in 44.0%, splenomegaly in 12.5%, and autosplenectomy in 48.5% of the SCDs patients. Although smoking was observed in 7.0% of the patients, there was only one case (0.3%) with regular alcohol consumption. Additionally, there were digital clubbing in 6.4%, COPD in 4.8%, leg ulcers in 12.8%, stroke in 7.0%, CRD in 8.6%, pulmonary hypertension in 11.8%, cirrhosis in 3.5%, CHD in 8.0%, and exitus in 5.7% of the cases with the SCDs. Prevalence of mortality were similar in both genders (5.2% versus 6.3% in females and males, respectively,  $p > 0.05$ ), and mean ages of the mortal cases were 32.1 versus 29.1 years in females and males, respectively ( $p > 0.05$ ) (Table 2). On the other hand, five of the CRD cases were on hemodialysis, and one with right renal transplantation. Histologic procedure for the diagnosis of cirrhosis was not required in any case. Although antiHCV was positive in two of the cirrhotics, HCV RNA was detected as negative by polymerase chain reaction in both. The solitary case of regular alcohol consumption was not cirrhotic at the time of study.

**Table 1: Sick cell patients with associated disorders**

Variables	Prevalence
Left renal atrophy	2.2% (7)
Right renal atrophy	0.3% (1) ( $p<0.001$ )*
Thalassemias	44.0% (137)
Splenomegaly	12.5% (39)
Autosplenectomy	48.5% (151)
Smoking	7.0% (22)
Regular alcohol consumption	0.3% (1)
Digital clubbing	6.4% (20)
Chronic obstructive pulmonary disease	4.8% (15)
Leg ulcers	12.8% (40)
Stroke	7.0% (22)
Chronic renal disease	8.6% (27)
Pulmonary hypertension	11.8% (37)
Cirrhosis	3.5% (11)
Coronary heart disease	8.0% (25)
Exitus	5.7% (18)

**Table 2: Features of the mortal cases**

Variables	Female cases	Male cases	<i>p</i> -value
Prevalence	5.2% (8)	6.3% (10)	ns*
Mean age (year)	32.1 ± 10.5 (19-45)	29.1 ± 9.6 (19-50)	ns

## Discussion

Nephrons are the basic functional units of the kidneys located in the renal parenchyma, and each kidney contains about one million nephrons. Renal atrophy is characterized by shrinkage of kidneys due to loss of nephrons. Loss of nephrons also causes shrinkages of the renal arteries and veins, secondarily. Renal diseases, urinary tract obstructions, or acute or chronic pyelonephritis may cause renal atrophy. Reflux nephropathy is characterized by renal damage due to the backflow of urine, and it may also cause renal atrophy. Renal atrophy may also be caused by the obstruction of urinary tract due to an increased pressure on it, or compression of the intrarenal veins or arteries. Obstructive uropathy causes a higher urinary pressure within the kidneys causing damage to the nephrons. Although the various etiologies, probably renal ischemia is the most frequent cause of the renal atrophy. Probably the most common cause of renal ischemia is the systemic atherosclerosis, and CRD due to the systemic atherosclerosis is common in elderlies. Although the younger mean ages, we detected CRD in 8.6% of all cases in the present study, since the SCDs are an accelerated systemic atherosclerotic process.

SCDs are accelerated systemic atherosclerotic processes (9) initiating at birth, and by which we can observe final consequences of the systemic atherosclerosis which began 30 or 40 years earlier in life. Actually name of the syndrome should be 'Rigid Cell Induced Chronic Endothelial Dysfunction' instead of the SCDs or sickle cell anemia since we cannot observe the sickle cells in the peripheric blood samples of cases with additional thalassemias, easily. On the other hand, the rigidity of the erythrocytes is the main problem instead of their shapes or severity of anemia. The rigid cells induced chronic endothelial damage causes tissue ischemia, infarction, and end-organ failures even in the absence of obvious vascular occlusions on the chronic background of damaged and edematous endothelium all over the body. Even there were patients with severe vision or hearing loss among the present study cases. The digital clubbing and recurrent leg ulcers may also indicate the chronic tissue hypoxia in such patients. Due to the reversibility of digital clubbing and leg ulcers with the hydroxyurea treatment, the chronic endothelial damage is probably prominent at the microvascular level as in diabetic microangiopathies, and reversible to some extent. Although large arteries and arterioles are especially important for blood carriage, capillaries are more important for tissue oxygenation. So passage of the rigid cells through the endothelial cells



cause damage on the capillaries. Reversibility of the process may probably be more in early years of life but it gets an irreversible nature over time. Thus endothelial cells all over the body are edematous and swollen due to the destructive process as in splenomegaly seen in early years of life. But the ischemic process terminates with tissue fibrosis and shrinkage all over the body as in autosplenectomy. Even there were four cases with total teeth loss and one case with right ovarian atrophy among the study cases. The solitary case of right renal atrophy may also be explained by the mechanism. On the other hand, anemia probably is not the cause of the end-organ failures in the SCDs, since we cannot observe any shortened survival in the thalassemia minor cases although the presence of a moderate anemia. Although the mean survivals were 42 and 48 years for males and females for the SCDs in the literature (15), they were 29.1 and 32.1 years in males and females in the present study, respectively. The great differences between the survival may be secondary to the initiation of hydroxyurea in infancy in such countries (16).

The accelerated atherosclerotic process can also affect the renal arteries, and may lead to poor perfusion of the kidneys leading to reduced renal function and failure. The right renal artery is longer than the left because of the location of the aorta, since the aorta is found on the left side of the body. Additionally, the right renal artery is lower than the left because of the lower position of the right kidney. So the left kidney possibly has a relatively higher arterial pressure due to the shorter distance to heart as an underlying cause of endothelial damage induced atherosclerosis. But according to our opinion, the accelerated atherosclerotic process alone cannot explain the significantly higher prevalence of renal atrophy on the left side (2.2% versus 0.3%,  $p < 0.001$ ) in the present study. The left renal atrophy has also been reported in the literature (17). On the other hand, the very high prevalences of associated thalassemias (44.0%) and splenomegaly (12.5%) with the SCDs cases may be important for the explanation, since spleen and left kidney are closely related organs which may also be observed with the development of varicose veins from the left renal vein at the splenic hilus in cirrhotic cases. Any pressure on the left kidney as in splenomegaly cases may cause torsion of the renal vein, and prevents its drainage. We especially think about the drainage problems at the venous level due to the much higher arterial pressure that cannot be obstructed easily and the much higher prevalence of varicocele in the left side in males (18-20).

Varicocele is a dilatation of pampiniform venous plexus within the scrotum. It occurs in 15-20% of all males and 40% of infertile males, since researchers documented a recurrent pattern of low sperm count, poor motility, and predominance of abnormal sperm forms in varicocele cases (21,22). Varicoceles are much more common (nearly 80% to 90%) in the left side due to several anatomic factors including angle at which the left testicular vein enters the left renal vein, lack of effective antireflux valves at the juncture of left testicular vein and left renal vein, the nutcracker syndrome, and some other left renal vein anomalies such

as passage behind the aorta. The nutcracker syndrome results mostly from the compression of the left renal vein between the abdominal aorta and superior mesenteric artery, although other variants exist (23). It may cause hematuria and left flank pain (24). Since the left gonad drains via the left renal vein, it can also result in left testicular pain in men or left lower quadrant pain in women (25). Nausea and vomiting may result due to compression of the splanchnic veins (25). An unusual manifestation of the nutcracker syndrome includes varicocele formation and varicose veins in the lower limbs (26). Another study has shown that the nutcracker syndrome is a frequent finding in varicocele patients (27), so it should be routinely searched in cases with left varicocele.

As a conclusion, the renal atrophy is significantly higher on the left side in the SCDs cases. Splenomegaly induced flow disorders in the left renal vessels, structural anomalies of the left renal vein including nutcracker syndrome and passage behind the aorta, and possibly the higher arterial pressure of the left kidney due to the shorter distance to heart as an underlying cause of endothelial damage induced atherosclerosis may be some of the possible causes. Because of the higher prevalences of left varicocele probably due to drainage of left testicular vein into the left renal vein, high prevalences of associated thalassemias with the SCDs as a cause of splenomegaly, and tissue ischemia and infarctions induced edematous splenomegaly in early lives of the SCDs cases, splenomegaly induced flow disorders of the left renal vein may be the most significant cause among them.

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