Leg ulcers in severity of sickle cell diseases

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ABSTRACT

Objective : Background: We tried to understand whether or not there are some positive correlations between leg ulcers and severity of sickle cell diseases (SCDs).

Methods: All patients with SCDs were taken into the study.

Results: The study included 346 patients with the SCDs (175 males). There were 50 cases (14.4%) with leg ulcers. Interestingly, the male ratio was significantly higher in patients with leg ulcers (74.0% versus 46.6%, p<0.001). Additionally, mean ages of the patients with leg ulcers were significantly higher than the patients without (35.0 versus 28.5 years, p<0.000). Prevalence of associated thalassemia minor was similar in both groups (64.0% versus 66.5%, respectively, p>0.05). On the other hand, smoking was significantly higher in patients with leg ulcers (28.0% versus 11.8%, p<0.05). Although the mean white blood cell and platelet counts of the peripheric blood were similar in both groups (p>0.05 for both), the mean hematocrit value was significantly lower in patients with leg ulcers (21.7% versus 24.0%, p= 0.002). On the other hand, although the painful crises per year, priapism, pulmonary hypertension, chronic obstructive pulmonary disease, coronary heart disease, rheumatic heart disease, and avascular necrosis of bones were all higher in patients with leg ulcers, the differences were only significant for digital clubbing, chronic renal disease, and stroke (p<0.05 for all).

Conclusion: SCDs are chronic destructive processes on capillaries initiating at birth, and terminate with early organ failures in life. Probably leg ulcers are found among the terminal consequences of the inflammatory processes that may indicate shortened survival.

Key words: Sickle cell diseases, leg ulcers, chronic capillary inflammation

Introduction

Atherosclerosis may be the major underlying cause of aging by inducing cellular hypoxia all over the body. As an example for the hypothesis, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in patients with pulmonary and/or cardiac diseases. Probably whole afferent vasculature including capillaries are involved in atherosclerosis. Some of the currently known accelerator causes of the systemic process are smoking, physical inactivity, and overweight for the development of terminal consequences including obesity, hypertension, diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and were researched under the title of metabolic syndrome in the literature (1-3). Similarly, sickle cell diseases (SCDs) are chronic destructive processes on capillaries. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably, loss of elasticity instead of shapes of RBCs is the major problem, since sickling is rare in the peripheric blood samples of SCDs patients with associated thalassemias, and human survival is not so affected in hereditary elliptocytosis or spherocytosis. Loss of elasticity is probably present in whole life, but exaggerated with conditions showing increased metabolic rate of the body. The hard RBCs may take their normal elastic natures after normalization of the metabolic rate, but they become hard bodies in time, permanently. The hard cells induced prolonged inflammation, edema, and fibrosis at capillary walls may terminate with tissue infarcts all over the body (4,5). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distributory functions of them. We tried to understand whether or not there are some positive correlations between leg ulcers and severity of SCDs.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and December 2014. All patients with SCDs were taken into the study. The SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Patients' medical histories including smoking habit, regular alcohol consumption, painful crises per year, operations, priapism, leg ulcers, and stroke were learnt. Cases with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A check up procedure including serum iron, total serum iron binding capacity, serum ferritin, serum creatinine, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure the systolic blood pressure (BP) of pulmonary artery, an abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (6). Cases with acute painful crises or any other inflammatory event were treated at first, and then the laboratory tests and clinical measurements were performed on the silent phase. Stroke is diagnosed by the computed tomography of brain. Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia in the patients (7). An x-ray film of abdomen in upright position was taken just in cases with abdominal distention and discomfort, vomiting, obstipation, and lack of bowel movement. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (8). Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent phase is accepted as pulmonary hypertension (9). CRD is diagnosed with a serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females during the silent phase. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, and histologic procedure in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0 and with the presence of Schamroth's sign (10,11). Associated thalassemia minors are detected with serum iron, total serum iron binding capacity, serum ferritin, and hemoglobin electrophoresis performed via HPLC. Stress electrocardiography is performed for cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Ileus was diagnosed by the General Surgeons with the consultations in case of indication. Eventually, cases with leg ulcers and without were collected into the two groups, and they were compared. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 346 patients with the SCDs (175 males and 171 females). There were 50 cases (14.4%) with leg ulcers. Interestingly, the male ratio was significantly higher in patients with leg ulcers (74.0% versus 46.6%, $p<0.001$). Additionally, mean ages of the patients with leg ulcers were significantly higher than the others (35.0 versus 28.5 years, $p<0.000$). Prevalence of associated thalassemia minor was similar in both groups (64.0% versus 66.5%, respectively, $p>0.05$). On the other hand, smoking was significantly higher in patients with leg ulcers (28.0% versus 11.8%, $p<0.05$) (Table 1). Although the mean white blood cell (WBC) and platelet (PLT) counts of the peripheric blood were similar in both groups ($p>0.05$ for both), the mean hematocrit (Hct) value was significantly lower in patients with leg ulcers (21.7% versus 24.0%, $p= 0.002$) (Table 2). On the other hand, although the painful crises per year, priapism, digital clubbing, pulmonary hypertension, COPD, CHD, CRD, rheumatic heart disease, avascular necrosis of bones, and stroke were all higher in patients with leg ulcers, the differences were only significant for digital clubbing, CRD, and stroke ($p<0.05$ for all), probably due to the small sample size of the group with leg ulcers (Table 3). Additionally, there were four patients with regular alcohol consumption who are not cirrhotic at the moment. Although antiHCV was positive in seven of the cirrhotics, HCV RNA was detected as positive just in two by polymerase chain reaction.

Table 1: Characteristic features of the study patients

Variables	Patients with leg ulcers	*p*-value	Patients without leg ulcers
Prevalence	14.4% (50)		85.5% (296)
Male ratio	***74.0% (37)***	***<0.001***	***46.6% (138)***
Mean age (year)	***35.0 ± 8.8 (16-58)***	***0.000***	***28.5 ± 9.9 (5-59)***
Thalassemia minors	64.0% (32)	Ns*	66.5% (197)
Smoking	***28.0% (14)***	***<0.001***	***11.8% (35)***

*Nonsignificant (p>0.05)

Table 2: Peripheric blood values of the study patients

Variables	Patients with leg ulcers	*p*-value	Patients without leg ulcers
Mean WBC* counts (µL)	14.792 ± 6.411 (6.870-36.900)	Ns†	15.114 ± 6.451 (1.580-39.200)
Mean Hct‡ value (%)	***21.7 ± 5.2 (11-34)***	***0.002***	***24.0 ± 4.8 (12-42)***
Mean PLT§ counts (µL)	445.810 ± 237.502 (56.000-1.142.000)	Ns	455.680 ± 227.874 (48.800-1.827.000)

*White blood cell †Nonsignificant (p>0.05) ‡Hematocrit §Platelet

Table 3: Associated pathologies of the study patients

Variables	Patients with leg ulcers	*p*-value	Patients without leg ulcers
Painful crises per year	5.2 ± 7.2 (0-36)	Ns*	5.0 ± 8.2 (0-52)
Tonsilectomy	4.0% (2)	Ns	5.4% (16)
Priapism	6.0% (3)	Ns	2.0% (6)
Ileus	2.0% (1)	Ns	2.3% (7)
Digital clubbing	***24.0% (12)***	***<0.001***	***7.0% (21)***
Pulmonary hypertension	16.0% (8)	Ns	10.8% (32)
COPD†	20.0% (10)	Ns	12.8% (38)
CHD‡	12.0% (6)	Ns	5.7% (17)
CRD§	***16.0% (8)***	***<0.05***	***7.0% (21)***
Rheumatic heart disease	10.0% (5)	Ns	6.0% (18)
Avascular necrosis of bones	26.0% (13)	Ns	20.2% (60)
Cirrhosis	4.0% (2)	Ns	4.3% (13)
Acute chest syndrome	2.0% (1)	Ns	4.7% (14)
Stroke	***16.0% (8)***	***<0.05***	***7.4% (22)***
Mortality	4.0% (2)	Ns	4.7% (14)

*Nonsignificant (p>0.05) †Chronic obstructive pulmonary disease ‡Coronary heart disease §Chronic renal disease

Discussion

Atherosclerosis is the most common type of vasculitis all over the world, and it is the leading cause of morbidity and mortality in elderlies. Probably the whole afferent vasculature including capillaries are involved in the body. Chronic endothelial injury and inflammation due to the much higher BP of afferent vasculature may be the major underlying cause, and efferent vessels are probably protected due to the much lower BP in them. Vascular walls become thickened due to the chronic endothelial injury, inflammation, edema, and fibrosis, and they lose their elastic natures which can decrease the blood flow and increase BP further. The hard RBCs induced chronic endothelial injury, inflammation, edema, and fibrosis mainly at the capillary level build up a prototype of an advanced atherosclerosis in younger ages in the SCDs.

SCDs are life-threatening genetic disorders affecting nearly 100,000 individuals in the United States (12). They keep vascular endothelium mainly at the capillary level (13), since the capillary system is the main distributor of the hard RBCs to tissues. In other words, SCDs are mainly chronic inflammatory instead of obstructive disorders, and the major problem is probably endothelial injury, inflammation, edema, and fibrosis rather than the hard RBCs induced occlusions in the capillary lumen. As a result, the lifespans of females and males with the SCDs were 48 and 42 years in the literature (14), whereas they were 33.3 and 29.9 years in the present study, respectively. The great differences may be secondary to initiation of hydroxyurea therapy much earlier in developed countries. On the other hand, the prolonged lifespan of females with SCDs and longer overall survival of females in the world cannot be explained by the atherosclerotic effects of smoking alone, instead it may be explained by more physical power requiring role of male sex in life (15,16).

Leg ulcers occur in 10 to 20% of patients with SCDs, and they are more common in males (17). The incidence increases with age and they are very rare before the age of 10 years (17). They are the most common in sickle cell anemia (HbSS) cases (17). They have an intractable nature, and around 97% of healed ulcers return in less than one year (18). The ulcers occur in distal areas with less collateral blood flow in the body (18). The most common location for these ulcers to develop is above the medial malleolus (the Gaiter area). The lateral malleoli are involved secondly in frequency. The pathogenesis of leg ulcers may be complex including mechanical obstruction by the hard RBCs, abnormal autonomic control with excessive vasoconstriction when in the dependent position, in situ thrombosis, anemia with decreased oxygen carrying capacity, and decreased nitric oxide bioavailability leading to impaired endothelial function (19,20). Venographic studies have shown that venous insufficiency is not a primary cause of the ulcers (17). Chronic damage to microcirculation of the skin via the hard RBCs is probably the major cause of leg ulcers in the SCDs (17). Increased exposure to the causative factors due to the blood pooling in the lower extremities by the effect of gravity may also explain the leg but not arm ulcers in the SCDs. Probably the same mechanism is also present for the diabetic ulcers, Buerger's disease, and varicose veins. On the other hand, smoking may have an additional role for the leg ulcers of the SCDs (21), since its atherosclerotic effects are well known in CHD, PAD, COPD, and cancers (22,23). The effects are the most obvious in COPD and Buerger's disease. Buerger's disease is an inflammatory process characterized by obliterative changes in small and medium-sized arteries, and it has never been reported in the absence of smoking. COPD may also be thought of as a localized Buerger's disease of the lungs. Similarly, smoking was higher in patients with leg ulcers in the present study (28.0% versus 11.8%, $p<0.05$) that may not be explained by the higher prevalence of smoking in men alone (22,23).

Hydroxyurea (hydroxycarbamide) is the only drug that was approved by Food and Drug Administration for the SCDs (12). It is an oral, cheap, safe, and highly effective drug for the SCDs that blocks cell division by suppressing formation of deoxyribonucleotides which are building blocks of DNA (13). Although the action of hydroxyurea is thought to be the increase of gamma globin synthesis for fetal hemoglobin (HbF) (24), its main action may be suppression of hyperproliferative WBCs and PLTs in the SCDs. Although there is presence of a continuous damage of hard RBCs on capillary endothelium, severity of the destructive process is probably exaggerated by the patients' own WBCs and PLTs. So mechanism of tissue damage of the SCDs may mimic autoimmune disorders, and suppression of excessive proliferation of patients' own WBCs and PLTs by the drug may limit the capillary endothelial injury, inflammation, edema, and fibrosis all over the body. Similarly, lower neutrophil counts were associated with lower crises rates, and if a tissue infarct occurs, lower neutrophil counts may decrease severity of pain and tissue damage (25). Furthermore, final HbF levels did not differ in hydroxyurea users (25). Due to the same reason, hydroxyurea is also used to suppress hyperproliferative cells in chronic myeloproliferative disorders and psoriasis, effectively. According to our practices during the eight-year period, the only side effect of hydroxyurea is a deep anemia. Although hydroxyurea increases Hct level in smaller doses, it may cause a deep anemia when used as a dose of 35 mg/kg/day. But this effect is usually harmless, and Hct level increases rapidly by decreasing the daily dose of the drug. On the other hand, although some authors suggest that hydroxyurea does not prevent or even augment the development of leg ulcers (26-28), some others have demonstrated that hydroxyurea is effective for the treatment of leg ulcers in the SCDs (29). According to our eight-year experiences again, due to the microvascular nature of the SCDs, as in microvascular complications of DM, complete healing of leg ulcers can frequently be achieved with hydroxyurea in children and adolescents, but it may be difficult due to the excessive fibrosis around the capillary walls later in life. Similarly, recalcitrant ulcers that have failed to epithelialize may benefit from an autologous skin graft. However, vascular insufficiency and circulatory difficulties lead to high rates of skin graft failure in the SCDs (29).

RBC transfusions are the most significant approach in severe acute conditions of the SCDs including acute chest syndrome, pulmonary hypertension, and stroke (30,31). Chronic transfusions are also used in the treatment of recalcitrant leg ulcers in the SCDs. If there is no healing after a period of six months,

transfusions are stopped. They decrease sickle cell concentrations in blood, suppress their production in bone marrow, and prevent hard RBCs induced endothelial injury, inflammation, edema, and fibrosis in brain, lungs, liver, bones, kidneys, and other organs (32,33). Since the main pathology is disseminated and prolonged tissue ischemia in the SCDs (34), simple and repeated RBCs transfusions are highly effective to restore tissue oxygenation. For example, ileus is also a common pathology in the SCDs' patients probably due to their atherosclerotic natures (35), and all of the ileus cases were able to be treated with simple and repeated RBCs transfusions in the present study. But transfusions have to be given early in ileus and other severe conditions rather than too late when the patient is clearly comatose. According to our experiences, simple and repeated RBC transfusions are superior to RBC exchange in the SCDs. First of all, simplicity of the procedure provides advantages to clinicians. Secondly, preparation of one or two units of RBC suspension in each time rather than preparation of several units provides time for clinicians to prepare more units by preventing sudden death of such patients. Thirdly, transfusion of RBC suspensions in secondary health centers can prevent some deaths developed during transport to tertiary centers for RBC exchange.

As a conclusion, SCDs are chronic destructive processes on capillaries initiating at birth, and terminating with early organ failure in life. Probably leg ulcers are found among the terminal consequences of the inflammatory processes that may indicate shortened survival.

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