Chronic endothelial inflammation and priapism in sickle cell diseases

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Abstract

Background: Sickle cell diseases (SCDs) are chronic destructive processes on endothelium, initiating at birth, all over the body. We tried to understand whether or not there is an association between chronic obstructive pulmonary disease (COPD) and priapism in the SCDs.

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

Results: The study included 411 patients with the SCDs (199 females). There were 60 patients with COPD (14.5%). Mean age of the patients was significantly higher in the COPD group (33.0 versus 29.5 years, P=0.005). The male ratio was significantly higher in the COPD group, too (80.0% versus 46.7%, P<0.001). Smoking was also higher in the COPD group, significantly (36.6% versus 9.9%, P<0.001). Parallel to the smoking, alcoholism was higher in the COPD group too (3.3% versus 0.8%, P<0.05). On the other hand, transfused red blood cell units in their lives (69.1 versus 32.9, P=0.001), priapism (10.0% versus 1.9%, P<0.001), leg ulcers (26.6% versus 11.6%, P<0.001), digital clubbing (25.0% versus 7.1%, P<0.001), coronary heart disease (26.6% versus 13.1%, P<0.01), chronic renal disease (16.6% versus 7.1%, P<0.01), and stroke (20.0% versus 7.9%, P<0.001) were all higher in the COPD group, significantly.

Conclusion: SCDs are chronic catastrophic processes on endothelium particularly at the arteriolar and venular level, and terminate with accelerated vascular damage induced end-organ failures in early years of life. There are highly significant associations between smoking, COPD, priapism, leg ulcers, digital clubbing, and stroke that may show a role of chronic endothelial inflammation in priapism in the SCDs.

Key words: Sickle cell diseases, chronic endothelial inflammation, chronic obstructive pulmonary disease, priapism

Introduction

Chronic endothelial damage induced atherosclerosis may be the major cause of aging by causing disseminated tissue hypoxia all over the body. For example, cardiac cirrhosis develops due to the prolonged hepatic ischemia in patients with pulmonary and/or cardiac diseases. Probably whole afferent vasculature including capillaries are involved in atherosclerosis. Some of the currently known accelerator factors of the inflammatory process are physical inactivity, overweight, smoking, and alcoholism for the development of irreversible end points including obesity, hypertension (HT), 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 death. They were researched under the issue of metabolic syndrome in the literature, extensively (1, 2). Similarly, sickle cell diseases (SCDs) are chronic catastrophic processes on endothelium particularly at the capillary level. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably, loss of elasticity instead of shape of RBCs is the major problem, since terminal sickling is very rare in the peripheric blood samples of the SCDs patients with associated thalassemia minors, and human survival is not so affected in hereditary elliptocytosis or spherocytosis. Loss of elasticity is probably present in whole lifespan, but exaggerated with increased metabolic rate of the body. The hard cells induced chronic endothelial inflammation, edema, and fibrosis mainly at the capillary level terminate with generalized tissue hypoxia all over the body in early years of life (3, 4). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution function of them. We tried to understand whether or not there is an association between COPD and priapism in the SCDs in the present study.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and July 2015. All patients with the SCDs were studied. The SCDs are diagnosed with the hemoglobin electrophoresis performed by means of high performance liquid chromatography (HPLC). Medical histories including smoking habit, regular alcohol consumption, painful crises per year, transfused RBC units in their lives, surgical operations, priapism, leg ulcers, and stroke were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. 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. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver 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 (5). 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 (6). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention and discomfort, vomiting, obstipation, and lack of bowel movement. Ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity of the abdomen. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent period is accepted as pulmonary hypertension (8). 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 period. Cirrhosis is diagnosed with liver function tests, ultrasonographic findings, and histologic procedure in case of requirement. 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 (9, 10). Associated thalassemia minors are detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Stress electrocardiography is just performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just 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. Ophthalmologic examination was performed according to the patients' complaints. Eventually, cases with COPD and without were collected into the two groups, and they were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 411 patients with the SCDs (199 females and 212 males). There were 60 patients with COPD (14.5%). Mean age of patients was significantly higher in the COPD group (33.0 versus 29.5 years, P=0.005). The male ratio was significantly higher in the COPD group, too (80.0% versus 46.7%, P<0.001). Smoking was also higher in the COPD group, significantly (36.6% versus 9.9%, P<0.001). Parallel to the smoking, alcoholism was higher in the COPD group, also (3.3% versus 0.8%, P<0.05). Prevalences of associated thalassemia minors were similar in the COPD group and other (71.6% versus 66.6%, respectively, P>0.05) (Table 1). On the other hand, transfused RBC units in their lives (69.1 versus 32.9, P=0.001), priapism (10.0% versus 1.9%, P<0.001), leg ulcers (26.6% versus 11.6%, P<0.001), digital clubbing

Table 1: Characteristic features of the study cases

Variables	Cases with COPD*	*P*-value	Cases without COPD
Prevalence	14.5% (60)		85.4% (351)
Male ratio	***80.0% (48)***	***<0.001***	***46.7% (164)***
Mean age (year)	***33.0 ± 10.0 (13-58)***	***0.005***	***29.5 ± 10.1 (5-59)***
Thalassemia minors	71.6% (43)	Ns†	66.6% (234)
Smoking	***36.6% (22)***	***<0.001***	***9.9% (35)***
Alcoholism	***3.3% (2)***	***<0.05***	***0.8% (3)***

*Chronic obstructive pulmonary disease †Nonsignificant (P>0.05)

Table 2: Associated pathologies of the study cases

Variables	Cases with COPD*	*P*-value	Cases without COPD
Painful crises per year	6.3 ± 8.7 (0-36)	Ns†	5.1 ± 8.4 (0-52)
Transfused RBC‡ units	***69.1 ± 89.1 (0-434)***	***0.001***	***32.9 ± 39.8 (0-250)***
Priapism	***10.0% (6)***	***<0.001***	***1.9% (7)***
Ileus	5.0% (3)	Ns	3.4% (12)
Cirrhosis	6.6% (4)	Ns	3.7% (13)
Leg ulcers	***26.6% (16)***	***<0.001***	***11.6% (41)***
Pulmonary hypertension	11.6% (7)	Ns	12.8% (45)
Digital clubbing	***25.0% (15)***	***<0.001***	***7.1% (25)***
CHD§	***26.6% (16)***	***<0.01***	***13.1% (46)***
CRD¶	***16.6% (10)***	***<0.01***	***7.1% (25)***
Rheumatic heart disease	8.3% (5)	Ns	5.1% (18)
Avascular necrosis of bones	20.0% (12)	Ns	24.2% (85)
ACS**	1.6% (1)	Ns	3.9% (14)
Stroke	***20.0% (12)***	***<0.001***	***7.9% (28)***
Mortality	8.3% (5)	Ns	5.9% (21)

*Chronic obstructive pulmonary disease †Nonsignificant (P>0.05) ‡Red blood cell §Coronary heart disease ¶Chronic renal disease **Acute chest syndrome

Table 3: Peripheric blood values of the study cases

Variables	Cases with COPD*	*P*-value	Cases without COPD
Mean WBC† counts (/µL)	15.796 ± 6.374 (6.600-36.900)	Ns‡	14.879 ± 6.670 (1.580-48.500)
Mean Hct§ values (%)	22.8 ± 6.0 (10-35)	Ns	23.7 ± 5.0 (8-42)
Mean PLT¶ counts (/µL)	433.071 ± 177.283 (113.000-1.142.000)	Ns	457.538 ± 236.171 (48.800-1.827.000)

*Chronic obstructive pulmonary disease †White blood cell ‡Nonsignificant (P>0.05) §Hematocrit ¶Platelet

(25.0% versus 7.1%, P<0.001), CHD (26.6% versus 13.1%, P<0.01), CRD (16.6% versus 7.1%, P<0.01), and stroke (20.0% versus 7.9%, P<0.001) were all higher in the COPD group, significantly (Table 2). The differences according to the mean white blood cell (WBC) counts, hematocrit (Hct) value, and platelet (PLT) counts of peripheric blood were nonsignificant between the two groups (P>0.05 for all) (Table 3). Beside these there were just three patients with sickle cell retinopathy in the group without COPD. There were 26 mortality cases during the nine-year follow up period, and 14 of them were males. The mean ages of mortality were 33.0 ± 9.6 (range 19-47) in females and 30.8 ± 8.9 years (range 19-50) in males (P>0.05). Additionally, there were four patients with HBsAg positivity (0.9%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR). Although antiHCV was positive in 25 cases of the study (6.0%), HCV RNA was detected as positive just in four (0.9%) by PCR.

Discussion

Chronic endothelial damage may be the most common type of vasculitis, and the leading cause of morbidity and mortality in the elderly. Probably whole afferent vasculature including capillaries are involved in the body. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent vessels are probably protected to some extent. Secondary to the prolonged endothelial damage induced fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that can reduce the blood flow and increase BP further. Although early withdrawal of the causative factors including

physical inactivity, excess weight, smoking, and alcoholism may prevent terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, the endothelial changes may not be reversed completely due to their fibrotic nature (11).

SCDs are life-threatening genetic disorders nearly affecting 100,000 individuals in the United States (12). As a difference from other causes of atherosclerosis, the SCDs probably keep vascular endothelium particularly at the capillary level (13), since the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial inflammation, edema, and fibrosis build up an advanced atherosclerosis in much younger ages of the patients (14). As another difference from other causes of endothelial damage, the SCDs probably keep vascular endothelium both at the arteriolar and venular level due to the hard RBCs. In other words, SCDs are mainly chronic inflammatory disorders, and probably the major problem is endothelial inflammation, edema, and fibrosis induced occlusions in the vascular walls rather than the lumens both at the arteriolar and venular level. As a result, the lifespans of patients with the SCDs were 48 years in females and 42 years in males in the literature (15), whereas they were 33.0 and 30.8 years in the present study, respectively. The great differences may be secondary to delayed initiation of hydroxyurea therapy and inadequate RBC supports in emergencies in our country.

COPD is an inflammatory disease that may mainly affect the pulmonary vasculature, and aging, excess weight, smoking, and alcoholism may be major underlying causes. The inflammatory process of endothelium is enhanced by release of various chemical factors by lymphocytes, and it terminates with fibrosis. Probably the accelerated atherosclerotic process is the main structural background of the functional changes characteristic of the disease. Although COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of an associated chronic endothelial inflammation all over the body (16, 17), and there may be close relationships between COPD, CHD, PAD, and stroke (18). In a multi-center study performed on 5,887 smokers aged between 35 and 60 years, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers, and CHD was the most common cardiovascular complication among them (19). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (19). In another study, 27% of all mortality cases were due to the cardiovascular causes in the moderate and severe COPD (20). Similarly, COPD may be one of the terminal consequences of the SCDs (21), and there were close relationships between COPD, priapism, leg ulcers, digital clubbing, and stroke in the SCDs in the present study.

Priapism is the painful erection of penis that does not return to its flaccid state within four hours in the absence of any stimulation (22). It is an emergency due to its potential complications. Damage to the blood vessels may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (22). It may be associated with hematological and neurologic disorders including SCDs, leukemia, thalassemia, Fabry's disease, spinal cord lesions, and spinal cord trauma (hanging victims) (23, 24). It may also be associated with glucose-6-phosphate dehydrogenase deficiency (G6PDD), which leads to decreased NADPH. NADPH is a co-factor involved in the formation of nitric oxide, thus G6PDD will lower nitric oxide levels, which may result in priapism. Ischemic (veno-occlusive, low flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial, high flow) are the three types of it (25). Ninety-five percent of clinically presented priapisms are the ischemic or low-flow disorders in which blood does not return adequately to the body from the penis as in the SCDs, and they are very painful (22, 25). The other 5% are nonischemic high-flow type usually caused by a blunt perineal trauma in which there is a short-circuit of the vascular system in the penis (22). Treatment of high-flow type is not as urgent as that of low-flow type since there is no risk of ischemia (22). For patients other than SCDs, oral pseudoephedrine or terbutaline may relax the stretched corporeal smooth muscles and increase permeability of erectile cavernous tissue that may permit easy flow of fluid from sinusoids into the venous system. If the drugs are not effective, aspiration of blood from the corpus cavernosum under local anesthesia is tried. If the aspiration also fails, distal shunts may cause the blood to leave the penis and return to circulation. Whereas in the SCDs, RBC support is the treatment of choice in the acute phase (26). RBC transfusions decrease sickle cell concentration in blood, suppress the bone marrow in production of abnormal RBCs, and eventually prevent further sickling induced damage to the penis. Whereas in the chronic phase, hydroxyurea should be the treatment of choice in priapism in the SCDs. It is the only drug that was approved by Food and Drug Administration for the treatment of 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). Its main action may be suppression of hyperproliferative WBCs and PLTs in the SCDs. Although 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 as in the autoimmune disorders. 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 (27). According to our experiences, hydroxyurea is an effective drug for prevention of attacks of priapism and its terminal consequences if it is iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls later in life.

Digital clubbing is a deformity of the finger and fingernails that is characterized by loss of normal <165° angle between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (28).

Schamroth's window test is a well-known test for the diagnosis (10). Some authors found clubbing in 0.9% of all patients admitted to the Department of Internal Medicine (9). Whereas the prevalences were much higher in the SCDs, and they were 13.2% in males and 6.0% in females (P<0.01) in the present study. The exact underlying cause of digital clubbing is not known, but chronic tissue hypoxia, vasodilation, secretion of growth factors, and some other mechanisms were proposed (29-32). Beside that, significance of digital clubbing is not well established. According to some authors, only 40% of digital clubbing cases turned out to have significant underlying diseases, while 60% remained well over the subsequent years (9). Whereas according to our experiences, it is frequently associated with pulmonary, cardiac, and hepatic disorders that are featuring with chronic tissue hypoxia, since lungs, heart, and liver are closely related organs that affect their functions in a short period of time (11). Similarly, hematologic disorders that are featuring with chronic tissue hypoxia may also terminate with digital clubbing. Smoking may also have a major role, since it takes significant roles in systemic atherosclerotic processes such as COPD, cirrhosis, CRD, PAD, CHD, stroke, and cancers (11, 33). Its atherosclerotic effects are the most obvious in Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels and capillaries, and it has never been reported in the absence of smoking. COPD may also be accepted as a localized Buerger's disease of the lungs. Similarly, there were highly significant associations between smoking, COPD, priapism, leg ulcers, digital clubbing, and stroke in SCDs cases in the present study (P<0.001 in all), and digital clubbing may be an indicator of disseminated vascular damage particularly at the capillary level in the SCDs.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (34), and the ratio was 13.8% in the present study. The incidence increases with age and they are rare under the age of 10 years (34). They are also common in males and sickle cell anemia (HbSS) cases (34). Similarly, there were 57 cases with leg ulcers, and 41 of them were males (19.3% in males versus 8.0% in females, P<0.001) in the present study. Additionally, mean age of the patients with leg ulcers was significantly higher than the others (34.8 versus 29.2 years, P<0.000). Leg ulcers have an intractable nature, and around 97% of healed ulcers return in less than one year (35). The ulcers occur in distal areas with less collateral blood flow in the body (35). Chronic endothelial inflammation particularly at the capillary level due to the hard RBCs may be the major cause in the SCDs (34). Prolonged 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 true for the diabetic ulcers, Buerger's disease, varicose veins, and onychomycosis. Smoking may also have some additional effects on the ulcers (36), since both of them are much more common in males (34), and strong atherosclerotic effects of smoking are well-known (33). Venous insufficiency may also accelerate the process by causing pooling of causative hard RBCs in the legs. According to our nine-year experiences, prolonged resolution of ulcers with hydroxyurea in early years of SCDs may also suggest that leg ulcers may actually be secondary to the increased WBC and PLT counts induced chronic endothelial inflammation rather than an irreversible damage. But later in life, it is difficult to heal completely due to the irreversible and fibrotic consequences of the prolonged endothelial inflammation.

Stroke is a common complication of the SCDs (37). Similar to the leg ulcers, stroke is also higher in the HbSS cases (38). Thromboembolism in the background of accelerated atherosclerosis is the most common cause of stroke in the normal population. Whereas in the SCDs, sickling induced disseminated endothelial injury, activations of WBC, PLT, and coagulation systems, and hemolysis may terminate with prolonged endothelial inflammation, edema, and fibrosis (39). Similarly, a higher WBC count is associated with a higher incidence of stroke (40). In other words, stroke may not have a macrovascular origin, instead disseminated and prolonged endothelial edema may be much more important in the SCDs. Infections, emotional stresses, trauma, and other inflammatory events may precipitate stroke, since increased metabolic rate may accelerate sickling and secondary endothelial edema. Similar to the number and severity of painful crises, priapism, and leg ulcers, a significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of strokes are secondary to the increased WBC and PLT counts induced prolonged and disseminated endothelial edema in the SCDs (13, 41).

As a conclusion, SCDs are chronic catastrophic processes on endothelium particularly at the arteriolar and venular level, and terminate with accelerated vascular damage induced end-organ failure in early years of life. There are highly significant associations between smoking, COPD, priapism, leg ulcers, digital clubbing, and stroke that may show a role of chronic endothelial inflammation in priapism in the SCDs.

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