Chronic obstructive pulmonary disease may be one of the terminal endpoints of the sickle cell diseases

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Abstract

Background: Sickle cell diseases (SCDs) are chronic destructive processes on vascular 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 severity of the SCDs.

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

Results: The study included 411 patients with the SCDs (199 females and 212 males). There were 60 patients (14.5%) with the COPD. 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 also higher among the COPD cases, significantly (3.3% versus 0.8%, P<0.05). Beside these, 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 among the COPD cases, significantly.

Conclusion: SCDs are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. COPD may be one of the terminal endpoints of the diseases.

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

Introduction

Chronic endothelial damage induced atherosclerosis may be the major cause of aging and death by causing disseminated tissue ischemia all over the body. For example, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in patients with pulmonary and/or cardiac diseases. Probably the whole afferent vasculature including capillaries are involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, weight gain, smoking, and alcohol intake for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Similarly, sickle cell diseases (SCDs) are chronic catastrophic processes on vascular 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 is the major problem, since sickling is rare in the peripheric blood samples of the SCDs patients associated with thalassemia minors, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is probably present in whole lifespan, but exaggerated with increased metabolic rate and various stresses of the body. The hard cells induced prolonged endothelial inflammation, remodeling, and fibrosis mainly at the capillary level terminate with disseminated tissue hypoxia all over the body (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 severity of SCDs in the present study.

Material and Methods

The study was performed in 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 via high performance liquid chromatography (HPLC) method. 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 by means of 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 or discomfort, vomiting, obstipation, or lack of bowel movement. 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 is accepted as pulmonary hypertension (8). CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Cirrhosis is diagnosed with findings of physical examination, 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 (9, 10). Associated thalassemia minors are detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC method. An exercise electrocardiogram is just performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram 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 is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity of the abdomen. 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 (14.5%) with the COPD. 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 among the COPD cases, significantly (36.6% versus 9.9%, P<0.001). Parallel to the smoking, alcoholism was also higher among the COPD cases, significantly (3.3% versus 0.8%, P<0.05). Prevalence of associated thalassemia minors were similar in both groups (71.6% versus 66.6% in the COPD group and other, respectively, P>0.05) (Table

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	6.2% (22)

*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

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 (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 among the COPD cases, 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 (P>0.05) between the two groups (Table 3). Beside these there were three patients with sickle cell retinopathy, all of them were found in cases without the COPD. There were 27 mortality during the nine-year follow up period, and 14 of them were males. The mean ages of mortality were 33.6 ± 9.5 (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) method. Although antiHCV was positive in 25 (6.0%) of the study cases, HCV RNA was detected as positive just in four patients by PCR method.

Discussion

Chronic endothelial damage induced atherosclerosis may be the most common type of vasculitis, and the leading cause of morbidity, mortality, and aging in human beings. Although it is much more common in the elderly, chronic inflammatory processes including SCDs, rheumatologic disorders, cancers, and chronic infections decrease the age of involvement. Probably the whole afferent vasculature including capillaries are involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent vascular endothelium are probably protected due to the much lower BP in them. Secondary to the chronic endothelial damage, inflammation, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures which reduce the blood flow and increase BP further. Although early withdrawal of the causative factors including physical inactivity, weight gain, smoking, and alcohol intake may prevent terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, the endothelial changes may not be reversed completely due to the fibrotic nature of them (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 to the tissues. The hard cells induced chronic endothelial damage, inflammation, and fibrosis build up, an advanced atherosclerosis in much younger ages of the patients. As a result, lifespans of the patients with SCDs were 48 years in females and 42 years in males in the literature (14), whereas they were 33.6 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. On the other hand, longer lifespan of females with the SCDs (14) and longer overall survival of females in the world (15) can not be explained by the atherosclerotic effects of smoking or alcohol alone, instead it may be explained by more physical power requiring role of male sex in life that may terminate with an exaggerated sickling and/or atherosclerosis all over the body (16).

COPD is the third leading cause of death with differing causes, pathogenic mechanisms, and physiological effects, worldwide (17). It is an inflammatory disease that may mainly affect the pulmonary vasculature, and aging, smoking, and excess weight may be major causes. As also observed in the present study, regular alcohol consumption may also take place in the inflammatory process. Similarly, COPD was one of the most frequent diagnoses in patients with alcohol dependence in another study (18). Additionally, 30-day readmission rate was higher in COPD patients with alcoholism (19). Probably the accelerated atherosclerotic process is the main structural background of functional changes characteristic of the COPD. The inflammatory process of endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with fibrosis, atherosclerosis, and pulmonary losses. Although COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of an associated endothelial inflammation all over the body (20, 21). For example, there may be a close relationships between COPD, CHD, PAD, and stroke in a previous study (22). Similarly, two-thirds of mortality were caused by cardiovascular diseases and lung cancers, and CHD was the most common one among them in a multi-center study performed on 5,887 smokers (23). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (23). In another study, 27% of all mortality was due to the cardiovascular causes in the moderate and severe COPD patients (24). As also shown in a previous study (25), COPD may be one of the terminal endpoints of SCDs due to the higher prevalences of priapism, leg ulcers, clubbing, CHD, CRD, and stroke in the group with COPD in the present study.

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (11, 26). 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 it has never been reported in the absence of smoking. Smoking induced endothelial damage probably affects pulmonary vasculature much more than the other organs due to the higher concentration of its products in the respiratory system. But it may even cause cirrhosis, CRD, PAD, CHD, stroke, and cancers with the transport of its products in the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. Although its strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with some weight loss (27), there may be an increased

energy expenditure during smoking (28), and nicotine may decrease caloric intake in a dose-related manner (29). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (30). Body mass index (BMI) seems to be the highest in former, the lowest in current, and medium in never smokers (31). Similarly, smoking may also show the weakness of volition to control eating, and prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (32). Additionally, although CHD were detected with similar prevalences in both sexes (26), smoking and COPD were higher in males against the higher prevalences of BMI and its consequences including dyslipidemia, HT, and DM in females. Probably tobacco smoke induced acute inflammation on vascular endothelium all over the body is the major cause of loss of appetite, since the body doesn't want to eat during fighting. On the other hand, when we thought of some antidepressant properties of smoking and alcohol, the higher prevalences of them may also indicate some additional stresses on male sex in life and shortened survival of them.

Regular alcohol consumption may also cause an endothelial inflammation all over the body (33). Similar to the tobacco smoke, alcohol leads to an increased proinflammatory cytokine secretion and reactive oxygen species (ROS) production by tissue macrophages that damage organs via oxidative stresses, and these effects lie far beyond lung and liver. Against harmful effects of the ROS, there are enzymatic and non-enzymatic antioxidants in the body. Enzymatic ones include catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase and non-enzymatic ones include glutathione, carotene, bilirubin, tocopherol, uric acid, and metal ions (34). In a previous study, both tobacco smoke and ethyl alcohol resulted in a change of glutathione levels in serum and tissues in rats, and tobacco smoke had the strongest effect on protein nitrozylation in the brain (34). Ethyl alcohol had effects on glutathione level in serum, kidney, and brain, and superoxide dismutase activity in the brain (34). Chronic endothelial effects of alcohol may even be seen in the absence of a significant liver disease. For example, erectile dysfunction was significantly higher among aborigines with the risk of alcohol dependence in another study (35). There was a significant increase in leukocyte adhesion after chronic alcohol exposition in pancreas, and histological changes and cytokine levels correlated with the duration of exposition in rats in another study (36). Probably, cirrhosis is also a capillary endothelial inflammation terminated with disseminated hepatic destruction (37), and it may even be accepted as a localized Buerger's disease of the liver caused by alcohol. Stromal cells including hepatic stellate and endothelial cells have been proposed to control the balance between hepatic fibrosis and regeneration, but chronic damage eventually leads to progressive substitution of hepatic parenchyma by scar tissue resulting with cirrhosis (38). Although atherosclerotic effects of alcohol are the most obvious on liver due to the highest concentrations of its products via the portal blood flow (33), alcohol may even cause COPD, digital clubbing, CRD, PAD, CHD, stroke, and cancers like other atherosclerotic endpoints by the transport of its products within the blood.

Digital changes may help to identify some systemic disorders within the body. For example, digital clubbing 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 (39). Some authors found clubbing in 0.9% of all patients admitted to the department of internal medicine (9), whereas the prevalence was 4.2% in both sexes in our university (11). The exact cause and significance is unknown but chronic tissue hypoxia induced vasodilation and secretion of growth factors have been proposed (40-43). In the above study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (9). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, and/or 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. Similarly, digital clubbing may be an indicator of disseminated atherosclerosis particularly at the capillary level in the SCDs, and we observed clubbing in 9.7% of all patients with the SCDs in the present study. In addition to the SCDs, the higher prevalences of smoking ($P<0.001$) and clubbing ($P<0.001$) in the COPD group may also indicate some additional roles of smoking and COPD on clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (44), and the ratio was 13.8% in the present study. The incidence increases with age, and they are also common in males and sickle cell anemia (HbSS) cases (44). Similarly, leg ulcers were found as 19.3% in males versus 8.0% in females ($P<0.001$) in the present study. Beside that, mean ages of the patients with leg ulcers were significantly higher than the others (34.8 versus 29.2 years, $P<0.000$). The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (45). As an evidence of their atherosclerotic natures, the leg ulcers occur in distal areas with less collateral blood flow in the body (45). Chronic endothelial damage particularly at the capillary level due to the hard RBCs may be the major cause in the SCDs (44). Prolonged exposure to the hard RBCs 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. As also observed in venous ulcers of the legs, venous insufficiencies may also accelerate the process by causing pooling of causative hard RBCs in the legs. Probably pooling of blood in the lower extremities is also true for the diabetic ulcers, Buerger's disease, digital clubbing, varicose veins, and onychomycosis. Beside the hard RBCs of the SCDs, smoking and alcohol may also have some additional roles for the leg ulcers since both of them are much more common in males, and their atherosclerotic effects are obvious particularly in COPD, Buerger's disease, and cirrhosis (44). According to our nine-year experiences, prolonged resolution of ulcers with hydroxyurea may also suggest that the ulcers may

be secondary to increased WBC and PLT counts induced disseminated endothelial edema particularly at the capillary level.

Stroke is also a common complication of the SCDs (47). Similar to the leg ulcers, it is higher in the HbSS cases (48). Moreover, a higher WBC count is associated with a higher incidence of stroke (49). Sickling induced endothelial injury and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, remodeling, and fibrosis in the brain (50). Stroke of the SCDs may not have a macrovascular origin, instead disseminated endothelial inflammation and edema may be much more important at the capillary level. Infection, inflammation, and various stresses may precipitate stroke, since increased metabolic rate may accelerate sickling and secondary endothelial edema. Similar to the leg ulcers, a significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of stroke is secondary to increased WBC and PLT counts induced disseminated endothelial edema in the SCDs (13, 51).

As a conclusion, SCDs are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. COPD may be one of the terminal endpoints of the diseases.

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