

Acute chest syndrome does not have a chronic inflammatory background in sickle cell diseases

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ABSTRACT

Background: Sickle cell diseases (SCDs) are chronic catastrophic processes on vascular endothelium initiating at birth all over the body. We tried to understand whether or not there is a chronic inflammatory background of acute chest syndrome (ACS) in the SCDs.

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

Results: The study included 411 patients (199 females). As one of the significant endpoints of SCDs, patients with chronic obstructive pulmonary disease (COPD) and without were collected into two groups. There were 60 patients (14.5%) with COPD. Mean age (33.0 versus 29.5 years, $P=0.005$) and male ratio (80.0% versus 46.7%, $P<0.001$) were higher in the COPD group. Smoking (36.6% versus 9.9%, $P<0.001$) and alcohol (3.3% versus 0.8%, $P<0.05$) were also higher among the COPD cases. 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, too. Interestingly, against the higher rates of the above problems in the COPD group, incidence of ACS was even lower among them, nonsignificantly (1.6% versus 3.9%, $P>0.05$).

Conclusion: SCDs cause severe chronic endothelial damage particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Probably ACS is a sudden onset event without any chronic inflammatory background in the SCDs.

Key words: Sickle cell diseases, acute chest syndrome, chronic endothelial damage

Introduction

Chronic endothelial damage may be the major cause of aging by causing disseminated tissue ischemia all over the body. For instance, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in individuals with pulmonary and/or cardiac diseases. Probably whole afferent vasculature including capillaries are mainly involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, weight gain, smoking, and alcohol for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral 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 the causes of severe chronic endothelial damage 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 is the major problem since sickling is very rare in peripheral blood samples of patients with associated thalassemia minors, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present in whole lifespan, but exaggerated with stresses induced increased metabolic rate of the body. The hard cells induce prolonged endothelial inflammation, edema, and fibrosis mainly at the capillary level and terminate with disseminated cellular hypoxia all over the body (3, 4). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to their transport instead of distribution function for the hard cells. We tried to understand whether or not there is a chronic inflammatory background of acute chest syndrome (ACS) in the SCDs.

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 SCDs were studied. The SCDs are diagnosed with hemoglobin electrophoresis performed via 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 crisis or another inflammatory event were treated at first, and 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. Associated thalassemia minors were detected with serum iron, iron binding

capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (5). ACS is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (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, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (7). 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 physical examination, hepatic function tests, ultrasonographic results, and tissue sample 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 (8, 9). 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. Avascular necrosis of bones is diagnosed by means of MRI (10). Stroke is diagnosed by the computed tomography of brain. Ophthalmologic examination was performed according to the patients' complaints. Eventually as one of the significant endpoints of the SCDs, 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 SCDs (199 females and 212 males). There were 60 patients (14.5%) with COPD. Mean age (33.0 versus 29.5 years, $P=0.005$) and male ratio (80.0% versus 46.7%, $P<0.001$) were higher in the COPD group. Smoking (36.6% versus 9.9%, $P<0.001$) and alcohol (3.3% versus 0.8%, $P<0.05$) were also higher among the COPD cases. 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 1). Beside these, 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. Interestingly, against the higher rates of above problems in the COPD group, incidence of ACS was even lower among them, nonsignificantly (1.6% versus 3.9%, $P>0.05$) (Table 2). The differences according to the mean white blood cell (WBC) count, hematocrit (Hct) value, and platelet (PLT) count of peripheral blood were nonsignificant between the two groups (Table 3). There were 27 mortalities (14 males) during the nine-year follow up period, and only two of them in the group without COPD were due to the ACS. The mean ages of mortality were

33.6 ± 9.5 years (range 19-47) in females and 30.8 ± 8.9 years (range 19-50) in males (P>0.05). On the other hand, there were three patients with sickle cell retinopathy; all of them were found in cases without COPD. 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 6.0% (25) of the study cases, HCV RNA was detected as positive just in four (0.9%) by PCR.

Table 1: Characteristic features of the study cases

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

*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)
<u>Transfused RBC‡ units</u>	<u>69.1 ± 89.1 (0-434)</u>	<u>0.001</u>	<u>32.9 ± 39.8 (0-250)</u>
<u>Priapism</u>	<u>10.0% (6)</u>	<u><0.001</u>	<u>1.9% (7)</u>
Ileus	5.0% (3)	Ns	3.4% (12)
Cirrhosis	6.6% (4)	Ns	3.7% (13)
<u>Leg ulcers</u>	<u>26.6% (16)</u>	<u><0.001</u>	<u>11.6% (41)</u>
Pulmonary hypertension	11.6% (7)	Ns	12.8% (45)
<u>Digital clubbing</u>	<u>25.0% (15)</u>	<u><0.001</u>	<u>7.1% (25)</u>
<u>CHD§</u>	<u>26.6% (16)</u>	<u><0.01</u>	<u>13.1% (46)</u>
<u>CRD¶</u>	<u>16.6% (10)</u>	<u><0.01</u>	<u>7.1% (25)</u>
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)
<u>Stroke</u>	<u>20.0% (12)</u>	<u><0.001</u>	<u>7.9% (28)</u>
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

Discussion

Chronic endothelial damage may be the most common type of vasculitis, and the leading cause of aging in human beings. Physical inactivity, weight gain, smoking, alcohol, prolonged infections, and chronic inflammatory processes such as SCDs, rheumatologic disorders, and cancers accelerate the process. Probably whole afferent vasculature including capillaries are mainly involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent 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 that reduce the blood flow and increase BP further. Although early withdrawal of the causative factors 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 natures of them (11).

SCDs are life-threatening genetic disorders affecting around 100,000 individuals in the United States (12). As a difference from other causes of chronic endothelial damage, the SCDs may 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, edema, and fibrosis build up an advanced atherosclerosis in much younger ages of the patients. As a result, average lifespans of the patients 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 severe crises 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) cannot be explained by the atherosclerotic effects of smoking and 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).

ACS is responsible for a considerable mortality in the SCDs (17). According to the literature, it occurs most often as a single episode, and a past history is associated with an early mortality. Similarly, all of 15 cases with ACS had only a single episode, and two of them in the group without COPD were fatal in spite of rigorous RBC and ventilation support and antibiotic therapy in the present study. The remaining 13 patients are still alive without a recurrence at the end of the nine-year follow up period. ACS is most common between the ages of 2 to 4 years, and its incidence decreases with aging (18). Parallel to the knowledge, its incidence was only 3.6% among the patients with an average age of 30.0 ± 10.1 years (range 5-59) in the present study. The decreased incidence with aging may be due to a high mortality during the first episode and an acquired immunity against various antigens with aging. On the other hand, ACS may also show inborn severity of the SCDs. For example, its incidence is higher in severe cases such as cases with sickle cell anemia (HbSS) and a higher WBC count (17, 18). Probably, ACS is a complex event, and the terminology of 'ACS' does not indicate a definite diagnosis but reflects clinical difficulty of defining a distinct etiology in the majority of such episodes. One of the major clinical problems lies in distinguishing between infection and infarction, and in establishing clinical significance of fat embolism. For example, ACS did not show an infectious etiology in 66% of episodes in the above studies (17, 18). Similarly, 12 of 27 episodes of ACS had evidence of fat embolism as the cause in another study (19). But according to our nine-year experiences, the increased metabolic rate during infections may terminate with ACS. In other words, ACS may be a complex sequel characterized by disseminated endothelial damage and fat embolism at the capillary level, not in the pulmonary vasculature alone, instead all over the body. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCDs indicating a significant reduction of ACS episodes with hydroxyurea suggests that a substantial number of episodes are secondary to capillary inflammation and edema (20). Similarly, we strongly recommend hydroxyurea therapy for all patients and that may also be a cause of the low incidence of ACS among our follow up cases. Additionally, some authors showed that antibiotics do not shorten the clinical course (21, 22), and RBC support must be given whenever there is evidence of clinical deterioration. RBC support has the obvious benefits of decreasing sickle cell concentration directly, and

suppressing bone marrow for production of the abnormal cells. So they prevent further sickling induced damage to the lungs and other organs. RBC support should be given early in the course since it has prophylactic benefit. According to our experiences, simple RBC transfusions are superior to exchange. First of all, preparation of one or two units of RBC suspensions each time, rather than preparation of six units or higher gives time to prepare more units by preventing sudden death of such cases. Secondly, transfusions of one or two units of RBC suspensions each time will decrease the severity of pain, and relax anxiety of the patients and their relatives in a short period of time. Thirdly, transfusion of RBC suspensions in secondary health centers may prevent some deaths that have developed during transport to tertiary centers for exchange.

COPD is the third leading cause of death with various underlying causes, worldwide (23). It is an inflammatory disease mainly affecting the pulmonary vasculature, and smoking, excess weight, and aging may be the major causes. As also seen 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 (24). Additionally, 30-day readmission rate was higher in COPD patients with alcoholism (25). Probably the accelerated atherosclerotic process is the main structural background of functional changes characteristic of the disease. The endothelial process is enhanced by release of various chemicals by inflammatory cells, and terminates with atherosclerosis, fibrosis, 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 (26, 27). For instance, it was shown in a previous study that there may be close relationships between COPD, CHD, PAD, and stroke (28). 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 (29). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (29). In another study, 27% of all mortality were due to the cardiovascular causes in the moderate and severe COPD patients (30). As also observed before (31), COPD may be one of the terminal endpoints of the SCDs due to the higher prevalence of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCDs cases with COPD.

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (11, 32). 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 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. Beside the strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with some

weight loss (33). There may be an increased energy expenditure during smoking (34), and nicotine may decrease caloric intake in a dose-related manner (35). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (36). Body mass index (BMI) seems to be the highest in former, the lowest in current, and medium in never smokers (37). 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 (38). Additionally, although CHD was detected with similar prevalences in both sexes, smoking and COPD were higher in males against the higher prevalences of BMI and its consequences including dyslipidemia, HT, and DM in females (32). 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 some antidepressant properties of smoking and alcohol, the higher prevalences of them in males may also indicate some additional stresses on male sex and shortened survival of them.

Digital changes may help to identify some systemic disorders in the body. For instance, digital clubbing is characterized by loss of normal $<165^\circ$ 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 (8), whereas the prevalence was 4.2% in the same department in our university (11). The exact cause and significance is not known 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 (8). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, or hepatic disorders that are featuring with chronic tissue hypoxia. 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 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 digital 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 HbSS cases and in males (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 higher than the patients without (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 a proof of their atherosclerotic natures, the leg ulcers occur in distal areas with less collateral blood flow in the body (45). The hard RBCs induced chronic endothelial damage particularly at the capillary level may be the major cause in the SCDs (44). Prolonged exposure to the hard cells due to blood pooling in the lower extremities may also explain the leg but not arm ulcers in the SCDs. As also detected in venous ulcers of the legs, venous

insufficiency may also accelerate the process by causing pooling of causative hard cells in the legs. Probably pooling of blood in the lower extremities may also have effects in the diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis. Beside the hard cells, smoking and alcohol may also have some additional effects for the leg ulcers since both of them are much more common in males, and their atherosclerotic effects are more obvious in COPD, Buerger's disease, and cirrhosis (44). According to our experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that they may be secondary to increased WBC and PLT counts induced disseminated endothelial inflammation and edema particularly at the capillary level.

Stroke is also a common complication of the SCDs (46). Similar to the ACS and leg ulcers, it is more common in the HbSS cases and in cases with a higher WBC count (47, 48). Sickling induced disseminated endothelial damage and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, and fibrosis in the brain (49). Stroke of the SCDs may not have a macrovascular origin instead disseminated endothelial inflammation and edema may be much more prominent at the capillary level. Infections, inflammations, and various stresses may precipitate stroke since increased metabolic rate during such events may precipitate sickling and endothelial edema. Similar to the ACS and 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 diseases (13, 20).

As a conclusion, SCDs cause severe chronic endothelial damage particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Probably ACS is a sudden onset event without any chronic inflammatory background in the SCDs.

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