

Original Article

Mortal quintet of sickle cell diseases

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Abstract: Background: Sickle cell diseases (SCDs) are chronic inflammatory processes on capillary level. We tried to understand some possible correlations between stroke and severity of SCDs. Methods: All patients with SCDs were taken into the study. Results: The study included 343 patients (174 males and 169 females). There were 30 cases (8.7%) with stroke. The mean ages were similar in both groups (32.5 versus 29.1 years in the stroke group and other, respectively, $P>0.05$). The female ratios were similar in both groups, too (43.3% versus 49.8%, respectively, $P>0.05$). Prevalences of associated thalassemia minors were also similar in them (73.3% versus 65.1%, respectively, $P>0.05$). Smoking was higher among the stroke cases, significantly (26.6% versus 13.0%, $P<0.05$). Mean white blood cell count, hematocrit value, and mean platelet count of the peripheric blood were similar in both groups ($P>0.05$ for all). On the other hand, although the painful crises per year, tonsilectomy, priapism, ileus, pulmonary hypertension, chronic obstructive pulmonary disease, coronary heart disease, chronic renal disease, rheumatic heart disease, avascular necrosis of bones, cirrhosis, and mortality were all higher in the stroke group, the differences were only significant for acute chest syndrome (ACS), digital clubbing, and leg ulcers ($P<0.05$ for all), probably due to the small sample size of the stroke group. Conclusion: SCDs and smoking are chronic destructive processes on endothelium, and both terminate with early organ failures in life. Probably smoking, digital clubbing, leg ulcers, ACS, and stroke are mortal quintet of the SCDs that may indicate shortened survival in such patients.

Keywords: Sickle cell diseases, smoking, chronic capillary inflammation

Introduction

Atherosclerosis may be the main cause of aging by inducing disseminated cellular hypoxia all over the body. As an instance 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 factors of the systemic process are physical inactivity, overweight, and smoking for the development of eventual consequences including obesity, hypertension, diabetes mellitus (DM), peripheral 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 deaths. They were researched under the title of metabolic

syndrome in the literature, extensively [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 main problem, since sickling is rare in the peripheric blood samples of the 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 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, remodeling, and fibrosis at capillary walls terminate with tissue infarcts all over the body [4, 5]. On the other hand, obvious vascular occlusions may not

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Table 1. Characteristic features of the study cases

Variables	Cases with stroke	p-value	Cases without stroke
Prevalence	8.7% (30)		91.2% (313)
Female ratio	43.3% (13)	Ns*	49.8% (156)
Mean age (year)	32.5 ± 11.8 (9-56)	Ns	29.1 ± 9.7 (5-59)
Thalassemia minors	73.3% (22)	Ns	65.1% (204)
Smoking	26.6% (8)	<0.05	13.0% (41)

*Nonsignificant ($P>0.05$).

develop in greater vasculature due to the transport instead of distribution function of them. We tried to understand some possible correlations between stroke and severity of SCDs.

Material and methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and November 2014. All patients with the SCDs were taken into the study. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking habit, regular alcohol consumption, painful crises per year, surgical 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, 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 [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 (ACS) 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 patients 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 one 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 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 [10, 11]. 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 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 is diagnosed with abdominal distention, vomiting, obstipation, cramps, gaseous distention of isolated segments of bowel, and with the absence of peristaltic activity of the abdomen. Eventually, cases with stroke and without were taken 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 343 patients with the SCDs (169 females and 174 males). There were 30 cases (8.7%) with stroke. The mean ages were similar in both groups (32.5 versus 29.1 years in the stroke group and other, respectively, $P>0.05$). The female ratios were similar in both groups, too (43.3% versus 49.8%, respectively,

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Table 2. Peripheral blood values of the study cases

Variables	Cases with stroke	p-value	Cases without stroke
Mean WBC* counts (μL)	14.292 ± 4.861 (7.310-26.020)	Ns†	15.151 ± 6.581 (1.580-39.200)
Mean Hct‡ value (%)	23.2 ± 5.0 (12-36)	Ns	23.7 ± 4.9 (11-42)
Mean PLT§ counts (μL)	383.070 ± 176.318 (114.000-955.000)	Ns	460.030 ± 232.897 (48.000-1.827.000)

*White blood cell, †Nonsignificant ($P>0.05$), ‡Hematocrit, §Platelet.

Table 3. Associated pathologies of the study cases

Variables	Cases with stroke	p-value	Cases without stroke
Painful crises per year	7.4 ± 11.4 (0-36)	Ns*	4.8 ± 7.6 (0-52)
Tonsilectomy	6.6% (2)	Ns	4.7% (15)
Priapism	3.3% (1)	Ns	2.5% (8)
Ileus	6.6% (2)	Ns	1.9% (6)
Leg ulcers	26.6% (8)	<0.05	13.0% (41)
Digital clubbing	26.6% (8)	<0.001	7.9% (25)
Pulmonary hypertension	20.0% (6)	Ns	10.5% (33)
COPD†	20.0% (6)	Ns	13.4% (42)
CHD‡	6.6% (2)	Ns	6.3% (20)
CRD§	10.0% (3)	Ns	7.9% (25)
Rheumatic heart disease	10.0% (3)	Ns	6.3% (20)
Avascular necrosis of bones	23.3% (7)	Ns	20.7% (65)
Cirrhosis	6.6% (2)	Ns	4.1% (13)
ACS¶	13.3% (4)	<0.01	3.5% (11)
Mortality	6.6% (2)	Ns	4.4% (14)

*Nonsignificant ($P>0.05$), †Chronic obstructive pulmonary disease, ‡Coronary heart disease, §Chronic renal disease, ¶Acute chest syndrome.

$P>0.05$). Prevalences of associated thalassemia minors were also similar in them (73.3% versus 65.1%, respectively, $P>0.05$). Interestingly, smoking was higher among the stroke cases, significantly (26.6% versus 13.0%, $P<0.05$) (Table 1). The mean white blood cell (WBC) count, hematocrit (Hct) value, and the mean platelet (PLT) count of the peripheral blood were similar in both groups ($P>0.05$ for all) (Table 2). On the other hand, although the painful crises per year, tonsilectomy, priapism, ileus, pulmonary hypertension, COPD, CHD, CRD, rheumatic heart disease, avascular necrosis of bones, cirrhosis, and mortality were all higher in the stroke group, the differences were only significant for digital clubbing, leg ulcers, and ACS ($P<0.05$ for all), probably due to the small sample size of the stroke group (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 one by polymerase chain reaction.

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 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 reduce the blood flow and increase BP further. But as also understood from the digital clubbing cases [12], the atherosclerotic process may initially affect the afferent capillary endothelium due to their weak natures, and it is not surprising that cessation of smoking before the development of eventual changes may terminate with resolution of nail changes. But after development of COPD, cirrhosis, CRD, CHD, PAD, or stroke, the vascular changes could not be reversed probably due to the irreversible fibrotic results on the endothelium. The same fact may also be true for the other causes of atherosclerosis including excess weight, increased serum glucose and lipids, and elevated arterial BP.

SCDs are life-threatening genetic disorders affecting approximately 100,000 individuals in the United States [13]. As in smoking, excess weight, increased serum glucose and lipids, and elevated arterial BP, the SCDs keep vascular endothelium mainly at the capillary level

[14], since the capillary system is the main distributor of the hard RBCs to tissues. The hard RBCs induced chronic endothelial injury, inflammation, edema, and fibrosis mainly at the capillary level build up an advanced atherosclerosis even in much younger ages in the SCDs. In other words, SCDs are mainly chronic inflammatory instead of obstructive disorders, and probably the main problem is endothelial injury, inflammation, edema, and fibrosis rather than the hard RBCs induced occlusions in the capillary lumen all over the body. As a result, the lifespans of females and males with the SCDs were 48 and 42 years in the literature [15], 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 at childhood and rapid and adequate RBC transfusions during emergent clinical conditions in such patients in the developed countries. On the other hand, longer lifespan of females with the SCDs and longer overall survival of females in the world can not be explained by the atherosclerotic effects of smoking alone, instead it may be explained by physical power requiring role of male sex in life [16, 17], since physical power induced increased metabolic rate may terminate with an exaggerated loss of elasticity of RBCs, and eventually with an increased capillary endothelial inflammation, edema, remodeling, and fibrosis.

In addition to the excess weight, increased serum glucose and lipids, and elevated arterial BP, smoking also has a major role in systemic atherosclerotic processes such as COPD, cirrhosis, CRD, PAD, CHD, stroke, and cancers [18, 19]. Its atherosclerotic effects are the most obvious in COPD and Buerger's disease. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels and capillaries probably due to their weak natures again, and it has never been reported in the absence of smoking. Probably COPD is also a capillary endothelial inflammation terminating with disseminated pulmonary destructon, and it may be accepted as a localized Buerger's disease of the lungs. Although the strong atherosclerotic effects, smoking in human being and nicotine administration in animals may be associated with some weight loss [20]. There may be increased energy expenditure during smoking

[21], and nicotine may decrease caloric intake in a dose-related manner after cessation of smoking [22]. Nicotine may lengthen intermeal time, and decrease amount of meal eaten in animals [23]. Body weight seems to be the highest in former, lowest in current and medium in never smokers [24], since smoking, as a pleasure in life, may also show the weakness of volition to control eating. Parallel to the above result, prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant indicator of metabolic syndrome in another study [25]. Additionally, although the CHD were detected with similar prevalences in both sexes [18], the prevalences of smoking and COPD were higher in males against the higher prevalences of body mass index and its consequences including white coat hypertension, hyperbetalipoproteinemia, hypertriglyceridemia, HT, and DM in females. Beside that, myocardial infarction is increased six-fold in women and three-fold in men with smoking [26]. So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite.

Digital clubbing may be an indicator of disseminated atherosclerosis, and it is characterized by bulbous enlargement of the distal phalanges due to the increase in soft tissue. Clubbing develops in the following steps; fluctuation and softening of the nailbed, loss of normal $<165^\circ$ angle between the nailbed and fold, increased convexity of the nail fold, thickening of the whole distal finger, and shiny aspect and striation of the nail and skin [27]. Schamroth's window test is a popular test for the diagnosis of clubbing [11]. When the distal phalanges of corresponding fingers of opposite hands are directly opposed, a diamond-shaped 'window' is normally apparent between the nailbeds. If this window is obliterated, the test is positive. Digital clubbing is seen with pulmonary, cardiac, and hepatic diseases that are featuring with chronic hypoxia [10, 12], since lungs, heart, and liver are closely related organs that affect their functions in a short period of time. On the other hand, hematologic disorders that are featuring with chronic hypoxia may also terminate with digital clubbing. For example, we observed digital clubbing in 9.6% of cases with the SCDs in the present study, and it was significantly higher in the stroke cases (26.6% versus 7.9%, $P<0.001$). Interestingly, only 33.3% of clubbing

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cases were females in the previous study [10]. Similarly, this ratio was only 18.2% in our study [12]. So the overall male predominance of clubbing may also indicate smoking and physical power induced accelerated atherosclerosis in male sex [12, 19].

Stroke is an important cause of death in Western countries, and thromboembolism in a background of atherosclerosis is the most common cause of it. Aging, male sex, smoking, increased serum glucose and lipids, elevated arterial BP, and excess weight are the major accelerator causes of the stroke. Stroke is also a common complication of the SCDs [28, 29]. The incidence of stroke is higher in sickle cell anemia (HbSS) [30], and a higher WBC count is associated with a higher incidence [31]. It is attributed to sickling induced endothelial injury, activations of WBC, PLT, and coagulation systems, hemolysis, and eventual chronic endothelial inflammation, edema, remodeling, and fibrosis [32]. Probably, stroke is a complex and terminal event in the SCDs. Stroke episodes may not have a macrovascular origin, and disseminated capillary inflammation induced endothelial edema may be much more important in the SCDs. Infections and other stressful conditions may precipitate stroke, since increased metabolic rate during such episodes may accelerate sickling, disseminated capillary damage, endothelial edema, remodeling, and fibrosis. A significant reduction of stroke with hydroxyurea [33] also suggests that a significant proportion of strokes is secondary to the increased WBC and PLT counts induced disseminated capillary damage [14].

Leg ulcers are seen in 10 to 20% of patients with the SCDs [34]. The incidence increases with age and they are rare under the age of 10 years [34]. Similar to the stroke, leg ulcers are also more common in males and HbSS cases [34]. They 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 collaterally blood flow in the body [35]. The most common location of the ulcers is just above the medial malleolus. The lateral malleoli are involved secondly in frequency. Venous insufficiency is not a primary cause of the ulcers [34]. Chronic damage to microcirculation of the skin via the hard RBCs is probably the major cause in the SCDs [34]. Prolonged expo-

sure 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 significant for the diabetic ulcers, Buerger's disease, and varicose veins. On the other hand, smoking may also have an additional role for the ulcers [36], since its atherosclerotic effects are well-known in COPD, CHD, PAD, and Buerger's disease [18, 19].

ACS is also responsible for considerable morbidity and mortality in the SCDs [37]. It usually occurs as a single episode, and a past history is associated with a higher risk of mortality. The disorder is the most common between the ages of two and four years, and its incidence decreases with age, gradually [38]. The decreased incidence may be due to the excess mortality of the ACS and fewer viral and bacterial episodes in the older age groups due to the acquired immunity. Similar to the stroke and leg ulcers, its incidence is more common in HbSS cases, and a higher WBC count is associated with higher incidences of ACS and stroke [31, 37, 38]. As in the stroke, ACS may be a complex and terminal event. One of the major clinical problems develops in distinguishing between infection, infarction, and fat embolism, for example, ACS did not show an infectious etiology in 66% of episodes [37]. Similarly, 12 of 27 episodes had evidence of fat embolism as the cause in another study [39]. But according to our experiences, the increased metabolic rate during an infection may terminate with the ACS, since the ACS probably is a terminal and complex sequel including disseminated endothelial damage and fat embolism at the capillary level all over the body. A significant reduction of ACS in those on hydroxyurea [33] also suggests that a substantial number of ACS episodes may be secondary to capillary damage by the inflammatory cells including WBCs and PLTs. Similarly, antibiotics did not shorten the clinical course according to the experiences of some authors [40, 41].

As a conclusion, SCDs and smoking are chronic destructive processes on endothelium, and both terminate with early organ failures in life. Probably smoking, digital clubbing, leg ulcers, ACS, and stroke are mortal quintet of the SCDs that may indicate shortened survival in such patients.

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Disclosure of conflict of interest

None.

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