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Original Article

Acute chest syndrome in severity of sickle cell diseases

Mehmet Rami Helvaci[1], Can Acipayam[2], Akin Aydogan[1], Seckin Akkucuk[1], Cem Oruc[1], Cumali Gokce[1]

[1]Medical Faculty of Mustafa Kemal University, Antakya; [2]Medical Faculty of Sutcu Imam University, Antakya

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Abstract: Background: Sickle cell diseases (SCDs) are chronic inflammatory processes on capillary level. We tried to understand whether or not there are some positive correlations between acute chest syndrome (ACS) and severity of SCDs. Methods: All patients with the SCDs were taken into the study. Results: The study included 337 cases (167 females). There were 15 patients (4.4%) with the ACS. The mean ages were similar in both groups (29.4 versus 29.7 years in the ACS group and other, respectively, $P > 0.05$). The female ratios were similar in both groups, too (60.0% versus 49.0%, respectively, $P > 0.05$). Additionally, prevalences of associated thalassemia minors were similar in them (66.6% versus 65.5%, respectively, $P > 0.05$). Smoking was higher in the ACS group (20.0% versus 13.9%), but the difference was nonsignificant ($P > 0.05$). Although the mean white blood cell count and hematocrit value of peripheric blood were higher in the ACS group, the mean platelet count was lower in them, but the differences were nonsignificant again ($P > 0.05$ for all). On the other hand, although the painful crises per year, tonsilectomy, priapism, ileus, digital clubbing, pulmonary hypertension, rheumatic heart disease, cirrhosis, stroke, and mortality were higher in the ACS group, the difference was only significant for the stroke ($P < 0.05$), probably due to the small sample size of the ACS group. Conclusion: SCDs are chronic destructive processes on capillaries iniatiating at birth, and terminate with early organ failures in life. Probably ACS is one of the terminal consequences of the inflammatory processes that may indicate shortened survival in such patients.

Keywords: Acute chest syndrome, sickle cell diseases, chronic capillary damage, atherosclerosis

Introduction

Probably atherosclerosis is the main cause of aging by inducing prolonged cellular hypoxia all over the body. Cardiac cirrhosis developed due to the prolonged hepatic hypoxia may be a supportive clinic for the hypothesis. Whole afferent vasculature including capillaries are probably affected in the process. Some of the well known accelerators of the systemic process are smoking, physical inactivity, overweight, white coat hypertension, dyslipidemia, and insulin resistance for the development of terminal illnesses including obesity, hypertension, diabetes mellitus (DM), peripheric artery disease, chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), cirrhosis, coronary heart disease (CHD), mesenteric ischemia, osteoporosis, stroke, and aging, all of which are searched under the title of metabolic syndrome in the literature [1-4]. Similarly, sickle cell diseases (SCDs) are chronic destructive processes on capillaries. SCDs are caused by homozygous inheritance of hemoglobin S (Hb S) that causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably, loss of elasticity of RBCs instead of their shapes is the chief problem, since sickling is rare in the peripheric blood samples of 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 is exaggerated with miscellaneous stresses. The hard RBCs may take their normal elastic natures after normalization of the stressful conditions, but they become hard bodies in time, permanently. The hard cells induced chronic capillary damage and tissue ischemia and infarcts are the terminal consequences [5, 6]. On the other hand, obvious vascular obstructions may not develop in greater vasculature due to the transport instead of distribution functions of them for the hard RBCs. We tried to understand whether or not there are some positive correlations between acute chest syndrome (ACS) and severity of SCDs.

Table 1. Characteristic features of the study cases

Variables	Cases with ACS*	*P*-value	Cases without ACS
Prevalence	4.4% (15)		95.5% (322)
Female ratio	60.0% (9)	Ns†	49.0% (158)
Mean age (year)	29.4 ± 7.6 (20-48)	Ns	29.7 ± 10.0 (5-59)
Thalassemia minors	66.6% (10)	Ns	65.5% (211)
Smoking	*20.0% (3)*	*Ns*	*13.9% (45)*

*Acute chest syndrome, †Nonsignificant ($P > 0.05$).

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and October 2014. All cases with SCDs were taken into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Their medical histories including smoking habit, regular alcohol consumption, painful crises per year, operations, priapism, leg ulcers, and stroke were learnt. Cases with a history of one pack-year were accepted as smokers, and one drink a day for one year were accepted as drinkers. ACS is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia in the SCDs patients [7]. A check up procedure including serum iron, total iron binding capacity, ferritin, creatinine on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiography, a Doppler echocardiography both to evaluate cardiac walls and valves and to measure the systolic blood pressure (BP) of pulmonary artery, an abdominal ultrasonography, a Doppler ultrasonography to evaluate the portal blood flow in required cases, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other body parts for avascular necrosis of bone were scanned according to the patients' complaints. So avascular necrosis of bone was diagnosed via MRI [8]. 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. X-rays of abdomen in upright position was taken just in cases with abdominal distention and discomfort, vomiting, obstipation, and lack of bowel movement. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% [9]. Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent phase is accepted as pulmonary hypertension [10]. CRD is diagnosed with a permanently elevated serum creatinine level which is higher than 1.3 mg/dL in males and 1.2 mg/dL in females on the silent phase. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, and histologic procedure in case of need. 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 Swamroth sign [11, 12]. Associated thalassemia minors are detected by serum iron, total iron binding capacity, ferritin, and the hemoglobin electrophoresis performed via HPLC. A stress electrocardiography is performed in cases with an abnormal electrocardiography and/or angina pectoris. A coronary angiography is obtained 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. Ileus was diagnosed by the General Surgeons with the consultations just in required cases. Eventually, cases with ACS 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 337 patients with SCDs (167 females and 170 males). There were 15 cases (4.4%) with ACS. The mean ages were similar in both groups (29.4 versus 29.7 years in the ACS group and other, respectively, $P > 0.05$). The female ratios were similar in both groups, too (60.0% versus 49.0%, respectively, $P > 0.05$). Additionally, prevalences of associated thalassemia minors were similar in them (66.6% versus 65.5%, respectively, $P > 0.05$). Smoking was higher in the ACS group (20.0% versus 13.9%), but the difference was nonsignificant ($P > 0.05$) (**Table 1**). Although the mean

Table 2. Peripheric blood values of the study cases

Variables	Cases with ACS*	*P*-value	Cases without ACS
*Mean WBC** counts (/μL)*	*16.620 ± 7.412 (10.100-38.800)*	*Ns†*	*15.012 ± 6.454 (1.580-39.200)*
Mean Hct‡ value (%)	23.8 ± 2.7 (20-28)	Ns	23.6 ± 5.0 (11-42)
Mean PLT§ counts (/μL)	402.330 ± 154.213 (223.000-852.000)	Ns	454.860 ± 232.833 (48.800-1.827.000)

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

Table 3. Associated pathologies of the study cases

Variables	Cases with ACS*	*P*-value	Cases without ACS
Painful crises per year	*6.8 ± 8.9 (0-24)*	*Ns**	*5.0 ± 8.1 (0-52)*
Tonsilectomy	*13.3% (2)*	*Ns*	*4.0% (13)*
Priapism	*6.6% (1)*	*Ns*	*2.4% (8)*
Ileus	*6.6% (1)*	*Ns*	*2.1% (7)*
Digital clubbing	*20.0% (3)*	*Ns*	*9.0% (29)*
Leg ulcers	6.6% (1)	Ns	14.9% (48)
Pulmonary hypertension	*20.0% (3)*	*Ns*	*11.1% (36)*
COPD†	6.6% (1)	Ns	13.3% (43)
CHD‡	0.0% (0)	Ns	6.8% (22)
CRD§	6.6% (1)	Ns	8.3% (27)
Rheumatic heart disease	*13.3% (2)*	*Ns*	*6.5% (21)*
Avascular necrosis of bone	20.0% (3)	Ns	21.1% (68)
Cirrhosis	*6.6% (1)*	*Ns*	*4.3% (14)*
Stroke	*26.6% (4)*	*< 0.05*	*8.0% (26)*
Mortality	*13.3% (2)*	*Ns*	4.3% (14)

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

white blood cell (WBC) count and hematocrit (Hct) value of peripheric blood were higher in the ACS group, the mean platelet (PLT) count was lower in them, but the differences were nonsignificant again ($P > 0.05$ for all) (**Table 2**). On the other hand, although the painful crises per year, tonsilectomy, priapism, ileus, digital clubbing, pulmonary hypertension, rheumatic heart disease, cirrhosis, stroke, and mortality were higher in the ACS group, the difference was only significant for the stroke ($P < 0.05$), probably due to the small sample size of the ACS 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 method.

Discussion

According to our experiences, 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 are affected in the body. Chronic endothelial damage due to the much higher BP of afferent vasculature may be the major underlying cause, and efferent vasculature are probably protected due to the much lower BP in them. Vascular walls become thickened, and they lose their elasticity, which can reduce or even obstruct blood flow. According to our experiences, hard RBCs induced chronic endothelial damage is another risk factor for atherosclerosis in the SCDs.

SCDs affect endothelium mainly at the capillary level [13], since the capillary system is the main distributor of the hard RBCs to tissues. Due to the microvascular nature of the SCDs, as in microvascular complications of DM, complete healing of leg ulcers can usually be achieved with hydroxyurea in children and adolescents, but it may be difficult due to the excessive fibrosis around the wounds later in life. Finally, the mean lifespan was 42 years in males and 48 years in females in the literature [14], whereas it was 29.9 and 33.3 years in the present study, respectively. The great differences may be secondary to initiation of hydroxyurea therapy just after birth in developed countries. Besides that, the prolonged lifespan of females with SCDs and the longer overall survival of females in the world can not be explained by the strong atherosclerotic effects of smoking alone, instead it may be explained by more physical power requiring role of male sex in life [15, 16].

ACS is responsible for considerable morbidity and mortality in the SCDs [17]. ACS occurs most often as a single episode, and a past history of an ACS is associated with an early mor-

tality. The disorder is the most common in the 2 to 4 years of age and gradually decreases with age [18]. 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. The incidence of ACS is more common in sickle cell anemia (Hb SS) cases, and a higher WBC count is associated with a higher incidence [17, 18]. Probably, ACS is a complex and terminal event, and the terminology of 'ACS' does not indicate a definite diagnosis but reflects the clinical difficulty of defining a distinct etiology in the majority of such episodes. One of the major clinical problems lie in distinguishing between infection and infarction and in establishing clinical significance of fat embolism. All ACS episodes do not have an infectious origin, and non-infectious causes must be searched carefully. For example, ACS did not show an infectious etiology in 66% of episodes [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 experiences, the increased basal metabolic rate due to an infectious agent may terminate with the ACS, and the ACS may be a terminal and complex sequel including disseminated endothelial damage and fat embolism at the capillary level all over the body. A preliminary result from the Multi-Institutional Study of Hydroxyurea in SCD, indicating a significant reduction of ACS in those on hydroxyurea, suggests that a substantial number of ACS episodes are secondary to capillary obstruction [20]. Some authors showed that antibiotic treatment does not shorten the clinical course [21, 22], and RBC transfusions must be given whenever there is evidence of clinical deterioration. RBC transfusions have the obvious benefits of decreasing sickle cell concentration directly and by suppressing the bone marrow in production of abnormal RBCs, and preventing further sickling induced damage to the lungs or other organs. RBC transfusions should be performed early in the course so that they have prophylactic benefit rather than late when the patient is clearly comatose. According to our experiences, simple RBC transfusions are superior to RBC exchange, since simplicity of preparation of RBC suspensions in a short period of time provides advantages to clinicians at first. Secondly, preparation of one or two units of RBC suspension in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such cases. Thirdly, preparation of RBC suspensions in secondary health centers can prevent some deaths developed during transport to tertiary centers for RBC exchange in such cases.

Painful crises are nearly pathognomonic symptoms for the SCDs, and they are precipitated by infection, operation, depression, and injuries. Although the crises may not be life threatening, directly [23], crises induced increased metabolic rate may cause multiorgan failures on the chronic inflammatory background of the SCDs [24]. The severe pain is probably caused by the exaggerated inflammation of capillary endothelium, and the increased WBC and PLT counts and decreased Hct values may show a chronic inflammatory process during whole their lives in such patients. Similar to our results, increased WBC counts even in the silent periods was an independent predictor of the disease severity [25, 26], and it was associated with an increased risk of stroke by inducing disseminated capillary damage in brain [27]. According to our experiences, simple and repeated RBC transfusions according to the need are highly effective during the severe crises both to relieve pain and to prevent sudden death that may develop secondary to the multiorgan failures on the chronic background of the diseases. Additionally, RBC transfusions are the most common preventive measure of stroke in such patients [28, 29]. As also observed in a previous study [30], ileus is also a common pathology in such patients probably due to their atherosclerotic and obstructive natures. Since the main pathology is the disseminated tissue ischemia in the SCDs [31], simple and repeated RBCs transfusions to restore tissue perfusion are highly effective. Similarly, all of the ileus cases were able to be treated with this approach in the above [30] and present study.

According to our experiences, hydroxyurea is a safe and highly effective drug for SCDs. It is an orally used and cheap drug. It blocks cell division by suppressing formation of deoxyribonucleotides which are building blocks of DNA. Although the action way of hydroxyurea is thought to be the increase of gamma globin synthesis for fetal hemoglobin (Hb F) [32], its primary action may be suppression of hyperproliferative cells, particularly the WBCs and PLTs in the SCDs. By this way, the chronic inflamma-

tion of the SCDs that initiated at birth on the capillary endothelial cells can be suppressed. Due to the same reason, hydroxyurea is also used to suppress hyperproliferative cells in chronic myeloproliferative disorders and psoriasis. Although presence of a continuous damage of hard RBCs on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' WBCs and PLTs. So mechanism of tissue damage of the SCDs may mimic autoimmune disorders. So suppression of excessive proliferation of patients' own WBCs and PLTs by hydroxyurea may limit the endothelial damage-induced tissue ischemia and infarcts all over the body. Similarly, lower neutrophil counts were associated with lower crises rates, and if a tissue infarction occurs, lower neutrophil counts may limit severity of pain and tissue destruction [33]. Furthermore, final Hb F levels did not differ with hydroxyurea therapy in users [33]. According to our practices during the eight-year period, only side effect of the drug is deep anemia. Although hydroxyurea increases Hct level in smaller doses, it may cause deep anemia when used as a dose of 35 mg/kg/day. But this effect is usually asymptomatic, and the Hct level increases rapidly by decreasing the daily dose.

As a conclusion, SCDs are chronic destructive processes on capillaries iniatiating at birth, and terminate with early organ failures in life. Probably ACS is one of the terminal consequences of the inflammatory processes that may indicate shortened survival in such patients.

Address correspondence to: Dr. Mehmet Rami Helvaci, Medical Faculty of the Mustafa Kemal University, Serinyol, Antakya 31100, Hatay, Turkey. Tel: 00-90-326-2291000 (Internal 3399); Fax: 00-90-326-2455654; E-mail: mramihelvaci@hotmail.com

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