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Original Article

Sickle cell diseases and ileus

Mehmet Rami Helvaci, Akin Aydogan, Seckin Akkucuk, Cem Oruc, Mustafa Ugur

Medical Faculty of The Mustafa Kemal University, Turkey

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Abstract: Background: We tried to understand whether or not there is an increased incidence of ileus in patients with sickle cell diseases (SCDs). Methods: All cases with SCDs were taken into the study. Results: The study included 325 patients (160 females). The mean ages were similar in both sexes (29.3 versus 29.8 years in females and males, respectively, $p > 0.05$). Incidence of ileus was higher in males, significantly (3.6% versus 1.2%, $p < 0.01$). All of the ileus cases were able to be treated with simple and repeated red blood cell (RBC) transfusions without any surgical procedure. Smoking was higher in males, too (21.8% versus 6.2%, $p < 0.001$). The mean hematocrit value was also higher in males, significantly (24.4% versus 23.0%, $p = 0.016$). RBC units transfused, digital clubbing, leg ulcers, pulmonary hypertension, chronic obstructive pulmonary disease, coronary heart disease, and chronic renal disease were all higher in males, too ($p < 0.05$ for all). On the other hand, although the general mortality, white blood cell and platelet counts of peripheric blood, painful crises per year, rheumatic heart disease, avascular necrosis of bone, cirrhosis, and stroke were all higher in males, the differences were nonsignificant probably due to the small sample sizes of the groups ($p > 0.05$ for all). Conclusion: Although the relatively young mean ages of the patients with SCDs, the very high incidences of ileus are probably due to the strong atherosclerotic and obstructive natures of the two pathologies, and ileus should be treated with simple and repeated RBC transfusions to restore bowel perfusion in such patients.

Keywords: Sickle cell diseases, ileus, atherosclerosis, chronic endothelial damage

Introduction

Atherosclerosis may be the main cause of aging by inducing prolonged cellular hypoxia in body. Cardiac cirrhosis developed due to the prolonged hypoxia may be an example for the hypothesis. Whole afferent vasculature including capillaries are probably involved with some extent in the process. Some of the well known accelerators of the systemic process are smoking, physical inactivity, overweight, white coat hypertension (WCH), dyslipidemia, and insulin resistance for the development of terminal illnesses including obesity, hypertension (HT), 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 collected under the title of metabolic syndrome [1-4]. Similarly, sickle cell diseases (SCDs) are chronic destructive process on endothelium keeping all microvascular systems of the body. SCDs are caused by homozygous inheritance of hemoglobin S that causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs) under oxidative stresses. Probably, loss of elasticity of the RBCs instead of their shapes is the major problem, since sickling is rare in the peripheric blood samples of SCDs patients with associated thalassemias, and human survival is not so affected in hereditary elliptocytosis or hereditary spherocytosis. Loss of elasticity is probably present in whole life, but is exaggerated with various 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 endothelial damage and tissue ischemia and infarcts are the terminal consequences. On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution functions of them for the hard bodies. We tried to understand whether or not there is an increased incidence of ileus in SCDs.

Table 1. Characteristic features of the sickle cell patients

Variables	Females	*p*-value	Males
Prevalence	49.2% (160)	Ns*	50.7% (165)
Mean age (year)	29.3 ± 9.6 (8-59)	Ns	29.8 ± 9.9 (5-58)
Thalassemia minors	60.0% (96)	Ns	67.2% (111)
Smoking	*6.2% (10)*	*< 0.001*	*21.8% (36)*
İleus	*1.2% (2)*	*< 0.01*	*3.6% (6)*
Mortality	3.7% (6)	Ns	6.0% (10)

*Nonsignificant ($p > 0.05$).

Material and methods

The study was performed in The Medical Faculty of The Mustafa Kemal University between March 2007 and June 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 painful crises per year, units of transfused RBCs in their lives, smoking habit, regular alcohol consumption, 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. A check up procedure including serum iron, total iron binding capacity, serum ferritin, serum creatinine value on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, 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 bone areas for avascular necrosis were scanned according to the patients' complaints. 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% [5]. Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent phase is accepted as pulmonary hypertension [6]. Avascular necrosis of bone was detected via MRI [7]. CRD is diagnosed with a permanently elevated serum creatinine level which is 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females on the silent phase. Cirrhosis is diagnosed with hepatic 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 Swamroth sign [8, 9]. Associated thalassemia minors are detected by serum iron, total iron binding capacity, serum 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. The diagnosis of ileus was given by the General Surgeons with the consultations just in required cases. Eventually, incidence of ileus was detected in females and males, the two groups 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 325 patients with SCDs (160 females and 165 males). The mean ages were similar in both sexes (29.3 versus 29.8 years in females and males, respectively, $p > 0.05$). Prevalences of associated thalassemia minors were similar in both sexes, too (60.0% versus 67.2% in females and males, respectively, $p > 0.05$). Incidence of ileus was higher in males, significantly (3.6% versus 1.2%, $p < 0.01$). Smoking was higher in males, too (21.8% versus 6.2%, $p < 0.001$). Although the general mortality was also higher in males, the difference was nonsignificant probably due to the small sample sizes of the groups (6.0% versus 3.7%, $p > 0.05$) (**Table 1**). The mean ages of mortality were 33.3 ± 8.5 (21-44) and 29.9 ±

Table 2. Peripheric blood values of the sickle cell patients

Variables	Females	*p*-value	Males
Mean WBC* counts (μL)	14.644 ± 6.288 (1.580-39.200)	Ns†	15.519 ± 6.728 (2.460-38.800)
Mean Hct‡ value (%)	*23.0 ± 3.9 (14-38)*	*0.016*	*24.4 ± 5.5 (11-42)*
Mean PLT§ counts (μL)	450.740 ± 190.903 (48.800-1.241.000)	Ns	455.030 ± 268.794 (56.000-1.827.000)

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

Table 3. Associated pathologies of the sickle cell patients

Variables	Females	*p*-value	Males
Painful crises per year	4.6 ± 7.9 (0-52)	Ns*	5.6 ± 8.1 (0-52)
RBC† units transfused	*27.3 ± 34.1 (0-200)*	*0.001*	*49.1 ± 61.4 (0-370)*
Digital clubbing	*6.8% (11)*	*< 0.05*	*11.5% (19)*
Leg ulcers	*8.1% (13)*	*< 0.001*	*20.6% (34)*
Pulmonary hypertension	*8.7% (14)*	*< 0.01*	*14.5% (24)*
COPD‡	*5.6% (9)*	*< 0.001*	*19.3% (32)*
CHD§	*3.7% (6)*	*< 0.01*	*7.8% (13)*
CRD¶	*4.3% (7)*	*< 0.001*	*10.9% (18)*
Rheumatic heart disease	5.6% (9)	Ns	8.4% (14)
Avascular necrosis of bone	20.0% (32)	Ns	21.2% (35)
Cirrhosis	3.1% (5)	Ns	5.4% (9)
Stroke	6.8% (11)	Ns	9.0% (15)

*Nonsignificant, ($p > 0.05$), †Red blood cell, ‡Chronic obstructive pulmonary disease, §Coronary heart disease, ¶Chronic renal disease.

9.0 (19-50) in females and males, respectively ($p > 0.05$). The white blood cell (WBC) and platelet (PLT) counts of peripheric blood were higher in males, too, but the differences were also nonsignificant probably due to the same reason above ($p > 0.05$ for both). On the other hand, the mean hematocrit (Hct) value was higher in males, significantly (24.4% versus 23.0%, $p = 0.016$) (**Table 2**). RBC units transfused, digital clubbing, leg ulcers, pulmonary hypertension, COPD, CHD, and CRD were all higher in males ($p < 0.05$ for all). Although the painful crises per year, rheumatic heart disease, avascular necrosis of bone, cirrhosis, and stroke were also higher in males, the differences were nonsignificant probably due to the same reason above ($p > 0.05$ for all) (**Table 3**). There were three patients with regular alcohol consumption who are not cirrhotic at the moment. Although antiHCV was positive in six of the cirrhotics, HCV RNA was detected as positive by polymerase chain reaction method just in one.

Discussion

Atherosclerosis may be the most common form of vasculitis all over the world. It affects brain, heart, kidneys, lungs, liver, bones, intestines, and extremities, 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 main 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 obstruct blood flow. According to our experiences, hard RBCs induced chronic endothelial damage in the SCDs is another strong risk factor for atherosclerosis.

Ileus is a transient arrest of intestinal peristalsis. It is most frequently caused by severe and sistemic infections, but it may also be caused by mesenteric ischemia in cases with arterial or venous injury [10, 11]. Patients show no passage of gas and feces with abdominal distention and discomfort. Auscultation reveals a silent abdomen. X-rays of abdomen in upright position show gaseous distention of isolated segments of the small and large bowels. Treatment involves continuous nasogastric suction and intravenous fluids and electrolytes in the absence of oral feeding. Laparotomy should be considered in cases persisting more than one week due to the possibility of any mechanical obstruction. As also observed in the present study, ileus is a common pathology in patients with SCDs probably due to its strong atherosclerotic and obstructive nature. Since the main pathology is the tissue ischemia in the SCDs [12], 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 present study.

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 in adults. 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 earlier in life in developed countries. On the other hand, the prolonged lifespan of females with SCDs and the longer general survival of females in the world [15] can not be explained by strong atherosclerotic effects of smoking alone, instead it may be explained by more physical power requiring role of male sex in life [16].

Painful crises are nearly pathognomonic for the SCDs, and they are precipitated by infections, operations, depressions, and injuries. Although the crises may not be life threatening directly [17], crises induced increased basal metabolic rate may cause multiorgan failures on the chronic background of the diseases [18]. 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 [19], and it was associated with an increased risk of stroke by inducing disseminated endothelial damage in brain [20]. According to our practice, simple and repeated RBC transfusions according to the requirement 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 them [21, 22]. Simplicity of preparation of RBC suspensions in a short period of time provides advantages to clinicians. Additionally, preparation of one or two units of RBC suspension in each time provides time to clinicians to prepare more units by preventing sudden death of such cases. By this way, some deaths developed during transport to tertiary centers for RBC exchange can also be prevented.

Hydroxyurea is an oral, cheap, safe, and effective drug for chronic myeloproliferative disorders and SCDs. 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) [23], its primary action may be suppression of hyperproliferative cells, particularly the WBCs and PLTs in the SCDs. By this way, the chronic inflammatory process of the SCDs that initiated at birth on the capillary endothelium can be suppressed with some extent. Due to the same reason, hydroxyurea is also used to suppress hyperproliferative skin cells in psoriasis. Although presence of a continuous damage of hard cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' WBCs and PLTs. So mechanism of tissue damage may mimic autoimmune diseases in the SCDs. So suppression of excessive proliferation of patients' 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 [24]. Furthermore, final Hb F levels did not differ with hydroxyurea therapy in users [24].

Smoking has a significant role in atherosclerosis and cancers [25, 26], and its atherosclerotic effects are the most obvious in COPD and Buerger's disease. Buerger's disease is a chronic inflammatory process characterized by obliterative changes particularly in small and medium-sized arteries, and it has never been documented without smoking. COPD may also be thought as a Buerger's disease of the lungs. On the other hand, although the strong atherosclerotic effects, smoking may be associated with weight loss [27]. There may be an increased energy expenditure in smokers [28], and nicotine patches may suppress appetite after smoking cessation [29]. Nicotine may lengthen intermeal time, and decrease eating in animals

[30]. Additionally, body weight seems to be the highest in former, the lowest in current and medium in never smokers [31]. Furthermore, smoking may be associated with postcessation weight gain, and the risk may be the highest during the first year [32]. Although CHD were detected with similar prevalences in both sexes, smoking and COPD were higher in males against the higher prevalences of body mass index (BMI) and its consequences in females including WCH, hyperbetalipoproteinemia, hypertriglyceridemia, HT, and DM [25, 26]. In another study, the incidence of myocardial infarction is increased sixfold in women and threefold in men in smokers probably due to the additionally increased BMI in women [33]. So smoking is probably a powerful atherscleroticrisk factor with some suppressor effects on appetite. But smoking, as a pleasure in life, may also show the weakness of volition to control eating, so it may indicate additional risks of increased BMI and its consequences. Parallel to the result, prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of metabolic syndrome in another paper [34].

As a conclusion, although the relatively young mean ages of the patients with SCDs, the very high incidences of ileus are probably due to the strong atherosclerotic and obstructive natures of the two pathologies, and ileus should be treated with simple and repeated RBC transfusions to restore bowel perfusion 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; Fax: 00-90-326-2455654; E-mail: mramihelvaci@hotmail.com

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