What a low prevalence of systemic lupus erythematosus in sickle cell diseases

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ABSTRACT

Background: **We tried to understand whether or not there is a lower prevalence of systemic lupus erythematosus (SLE) due to an immunosuppression in the sickle cell diseases (SCDs).**

Methods: All patients with the SCDs and age and sex-matched controls were studied.

Results: **The study included 428 patients with the SCDs (220 males) and 433 controls (223 males). Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, p>0.05). Both smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were higher in males with the SCDs (p<0.001 for both). Although SLE was diagnosed in 6.0% of the control cases (24 females and two males), this ratio was only 0.4% (one female and one male) in the SCDs patients (p<0.001). On the other hand, transfused units of red blood cells in their lives (47.6 versus 28.4, p=0.000), chronic obstructive pulmonary disease (25.4% versus 7.2%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (7.2% versus 1.9%, p<0.001), leg ulcers (20.0% versus 7.2%, p<0.001), digital clubbing (14.0% versus 6.2%, p<0.001), coronary artery disease (18.1% versus 12.9%, p<0.05), chronic renal disease (10.4% versus 6.2%, p<0.05), and stroke (12.2% versus 7.6%, p<0.05) were all higher in males with SCDs.**

Conclusion: **SCDs are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failure in early years of life. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms that may be the cause of the lower prevalence of SLE in the SCDs.**

Key words: **Systemic lupus erythematosus, sickle cell diseases, chronic endothelial damage, immunosuppression**

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Introduction

Chronic endothelial damage may be the major cause of aging and associated morbidity and mortalities by causing disseminated tissue hypoxia all over the body. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause, and probably whole afferent vasculature including capillaries are involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, excess weight, smoking, and alcohol for the development of irreversible consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature (1, 2). Similarly, sickle cell diseases (SCDs) are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failure in early years of life. 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 main problem since sickling is rare in peripheric blood samples of the SCDs cases with associated thalassemia minor, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with increased metabolic rate of the body. The hard RBCs induced severe and continuous vascular endothelial inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (3, 4). Capillary systems may mainly be involved in the process due to their distribution function for the hard bodies. We tried to understand whether or not there is a lower prevalence of systemic lupus erythematosus (SLE) due to an immunosuppression in the SCDs.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and April 2016. All patients with the SCDs and age and sex-matched controls were studied. The SCDs were diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories of SCDs patients including smoking habit, regular alcohol consumption, painful crises per year, transfused units of RBCs in their lives, surgical operations, leg ulcers, and stroke were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist. 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, hepatic function tests, markers of hepatitis viruses A, B, 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 systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, 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 minor was detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. SLE is classified with the criteria of American College of Rheumatology of 1997 (5). In differential diagnosis, patients with rheumatoid arthritis (RA) were classified with the criteria of early rheumatoid arthritis (ERA) (6). The ERA criteria includes a morning stiffness of 30 minutes or longer, arthritis of three or more joint areas, arthritis of hand joints, positivity of rheumatoid factor, and positivity of anti-cyclic citrullinated peptide antibody. RA is defined by the presence of three or more of the criteria. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). 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 (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 physical examination, liver function tests, ultrasonographic evaluation, and tissue samples 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). An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CAD 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 (11). Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, prevalence of RA was detected both in the SCDs and control groups. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 428 patients with the SCDs (220 males) and 433 age and sex-matched control cases (223 males), totally. Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, $p>0.05$). Mean ages of the control cases were 30.4 versus 30.3 years, respectively ($p>0.05$ for both). Prevalence of associated thalassemia minor was similar in males and females with the SCDs (72.2% versus 67.7%, respectively, $p>0.05$). Both smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were significantly higher in males with the SCDs ($p<0.001$ for both) (Table 1). Although SLE was diagnosed in 6.0% of the control cases (24 females and two males), this ratio was only 0.4% (one female and one male) in the SCDs group ($p<0.01$) (Table 2). In other words, 89.2% of all SLE patients were female. The mean ages of SLE

Table 1: Characteristic features of the sickle cell patients

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Prevalence	51.4% (220)	Ns†	48.5% (208)
Mean age (year)	30.6 ± 10.1 (5-58)	Ns	30.1 ± 9.9 (8-59)
Thalassemia minors	72.2% (159)	Ns	67.7% (141)
Smoking	***24.0% (53)***	***<0.001***	***6.2% (13)***
Alcoholism	***5.0% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases
†Nonsignificant (p>0.05)

Table 2: Comparison of the patient and control groups

Variables	Patients with SCDs*	*p*-value	Control cases
Number	428	Ns†	433
Female ratio	48.5% (208)	Ns	48.4% (210)
Mean age of males	30.6 ± 10.1 (5-58)	Ns	30.4 ± 11.1 (9-59)
Mean age of females	30.1 ± 9.9 (8-59)	Ns	30.3 ± 10.4 (9-58)
Prevalence of SLE‡	***0.4% (2)***	***<0.001***	***6.0% (26)***

*Sickle cell diseases
†Nonsignificant (p>0.05)
‡Systemic lupus erythematosus

Table 3: Associated pathologies of the sickle cell patients

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBCs‡	***47.6 ± 61.6 (0-434)***	***0.000***	***28.4 ± 35.8 (0-206)***
COPD§	***25.4% (56)***	***<0.001***	***7.2% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Cirrhosis	***7.2% (16)***	***<0.001***	***1.9% (4)***
Leg ulcers	***20.0% (44)***	***<0.001***	***7.2% (15)***
Digital clubbing	***14.0% (31)***	***<0.001***	***6.2% (13)***
CAD¶	***18.1% (40)***	***<0.05***	***12.9% (27)***
CRD*	***10.4% (23)***	***<0.05***	***6.2% (13)***
Stroke	***12.2% (27)***	***<0.05***	***7.6% (16)***
Pulmonary hypertension	12.7% (28)	Ns	12.5% (26)
Varices	8.6% (19)	Ns	5.7% (12)
Rheumatic heart disease	6.8% (15)	Ns	5.7% (12)
Avascular necrosis of bones	25.0% (55)	Ns	25.0% (52)
Sickle cell retinopathy	0.9% (2)	Ns	0.4% (1)
Mortality	7.2% (16)	Ns	6.7% (14)

*Sickle cell diseases
†Nonsignificant (p>0.05)
‡Red blood cells
§Chronic obstructive pulmonary diseases
¶Coronary artery disease
**Chronic renal disease

cases were 37.0 ± 13.6 (17-58) and 36.5 ± 3.5 (34-39) years in the control and SCDs groups, respectively. On the other hand, transfused RBCs in their lives (47.6 versus 28.4 units, p=0.000), COPD (25.4% versus 7.2%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (7.2% versus 1.9%, p<0.001), leg ulcers (20.0% versus 7.2%, p<0.001), digital clubbing (14.0% versus 6.2%, p<0.001), CAD (18.1% versus 12.9%, p<0.05), CRD (10.4% versus 6.2%, p<0.05), and stroke (12.2% versus 7.6%, p<0.05) were all higher in males with the SCDs, significantly. There were two cases with sickle cell retinopathy in males and one in females (p>0.05). There were 30 mortality cases (16 males) during the ten-year follow-up period. The mean ages of mortality were 30.8 ± 8.3 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (p>0.05) (Table 3). Beside these, 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 5.8% (25) of the study cases, HCV RNA was detected as positive just in three (0.7%) by PCR.

Discussion

Chronic endothelial damage may be the leading cause of early aging and related morbidity and mortalities in human beings. Physical inactivity, excess weight, smoking, alcohol, chronic inflammatory and infectious processes, and cancers may accelerate the process. Probably, it is the most common type of vasculitis all over the world. Whole afferent vasculature including capillaries may mainly be involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the continuous endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature that reduces blood flow and increases systolic BP further. Although early withdrawal of the causative factors may retard the final consequences, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed completely due to their fibrotic nature (12).

SCDs are life-threatening hereditary disorders affecting around 100,000 individuals in the United States (13). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (14), because the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced severe and continuous endothelial damage, inflammation, edema, and fibrosis terminate with end-organ failure in early years of ages. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature (15), whereas they were 33.3 and 30.8 years in the present study, respectively. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBCs support during medical and surgical emergencies in the Hatay region of Turkey. Actually, RBCs support must be given during all medical and surgical emergencies in which there is evidence of clinical deterioration in the SCDs (16, 17). RBCs supports decrease sickle cell concentration in the circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling induced endothelial damage all over the body during such events. According to our 18-year experiences, simple RBCs transfusions are superior to the exchange. First of all, preparation of one or two units of RBCs suspensions at each time rather than preparation of six units or higher provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusion of one or two units of RBCs suspensions at each time decreases the severity of pain and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusions of lesser units of RBCs suspensions at each time decreases transfusion-related complications in the future. Fourthly, transfusions of RBCs suspensions in the secondary health centers prevents some deaths which have developed during transport to the tertiary centers for the exchange. Fifthly, transfusions of RBCs suspensions in the secondary health centers prevents some extra costs on the health system developed during the exchange in the tertiary centers. On the other hand, longer survival of females in the SCDs (15) and longer overall survival of females in the world (18) cannot be explained by the atherosclerotic effects of smoking and alcohol alone, instead it may be explained by higher physical efforts of male sex in life that may terminate with an exaggerated sickling and vascular endothelial damage in early years of life (19).

SLE is an autoimmune disease characterized by skin lesions on sun-exposed areas, oral lesions, nonerosive arthritis, fever, positive antibodies to double-stranded DNA, renal and central nervous system (CNS) involvement, and cytopenias (20). It is mostly seen in women with a younger mean age (20). Similarly, 89.2% of all SLE patients were female, and the mean age of SLE cases was 37.0 years in the present study. Like Hatay region of Turkey, the prevalence of SLE is higher than RA in some areas (6.0% versus 2.7%, p<0.001) (21), and higher prevalence of marriage with close relatives may be an underlying cause. The sera of most patients contain antinuclear antibodies (ANA), often including anti-double-stranded DNA antibodies (22). Articular symptoms are seen in 90% of patients, and they may exist for years before the diagnosis (23). For example, the average time from the onset of symptoms to diagnosis was 5 years in the above study (20). As a difference from RA, most lupus polyarthritis is non-destructive in nature. Cutaneous lesions include characteristic malar butterfly erythema, discoid lesions, and erythematous, firm, maculopapular lesions of face, sun-exposed areas of neck, upper chest, and elbows. Photosensitivity is seen in 40% of cases. Generalized lymphadenopathy is also common. CNS involvement may cause personality changes, stroke, epilepsy, and psychoses (24). Renal involvement may be silent or even fatal. The most common manifestation is proteinuria (25). There were increases in the incidence of renal involvement and neurological symptoms throughout the disease course (20). Diagnosis of SLE requires highly trained specialists who are able to differentiate early symptoms of SLE from other pathologies. For example, early-stage SLE can be difficult to differentiate from RA if arthritic symptoms predominate (26-28). Thus, although RA and SLE have similar agents in the treatment protocol, ANA and anti-double-stranded DNA antibodies should be studied in every patient with RA (29, 30). Clinicians in the Hematology Clinics should be aware of SLE due to the frequent thrombocytopenia in differential diagnosis, particularly with idiopathic thrombocytopenic purpura. Immunosuppression therapy has made it possible to control the disease with improved life expectancy and quality of life (25). According to our observations,

methotrexate may be the simplest, cheapest, orally used, and one of the most effective treatment regimens for both SLE and RA. It can suppress inflammation and reduce corticosteroid doses. Its benefit begins in 3 to 4 weeks. It can be given 2.5 to 20 mg in a single dose once weekly, starting with 7.5 mg/wk and gradually increased as needed.

SCDs are severe inflammatory processes terminating with major health problems in early years of life (31). For example, menarche is retarded in females with the SCDs (32). Additionally, the severe and continuous endothelial inflammation all over the body causes an overlapping chronic disease anemia. Furthermore, end-organ insufficiencies can even suppress the immune system of the patients. Acute sinusitis, tonsillitis, and urinary tract infections are the common causes of painful crises and hospitalization, and they can rapidly progress into the severe and life-threatening infections including pneumonia, meningitis, and sepsis due to the relative immunosuppression in such patients (33). For example, tonsillary hypertrophy is a frequent physical examination finding that may be the result of a prolonged infectious process due to the relative immunosuppression in such patients (34). Severe and prolonged endothelial inflammation induced prominent weight loss and cachexia are also common in them (4). Autosplenectomy, painful crises, hospitalizations, invasive procedures, RBCs supports, medications, prevented normal daily activities, and an eventually suppressed mood of the body can even suppress the immune system (35, 36). In another definition, SCDs may cause an immunosuppression with several mechanisms in the human body.

As a conclusion, SCDs are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failures in early years of life. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms that may be the cause of significantly lower prevalence of SLE in the SCDs.

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