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Stroke in Severity of Sickle Cell Diseases

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Abstract

Background: Sickle cell diseases (SCDs) are chronic inflammatory process on capillary level. We tried to understand whether or not there are some positive correlations between stroke and severity of SCDs.

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

Results: The study included 343 patients (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, 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 (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 digital clubbing, leg ulcers, and acute chest syndrome (p<0.05 for all), probably due to the small sample size of the stroke group.

Conclusion: SCDs are chronic destructive process on capillaries iniatiating at birth, and terminate with early organ failures in life. Probably stroke is one of the terminal consequences of the inflammatory process that may indicate shortened survival in such cases.

Keywords: Sickle cell diseases; Stroke; Chronic capillary inflammation; Atherosclerosis

Introduction

Atherosclerosis may be the most significant underlying cause of aging by inducing prolonged cellular hypoxia all over the body. As an example for the hypothesis, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in patients with pulmonary and/or cardiac diseases. Whole afferent vasculature including capillaries is probably involved in atherosclerosis. Some of the currently known accelerators of the systemic process are smoking, physical inactivity, and overweight for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease, chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, stroke, and aging, all of which are researched under the title of metabolic syndrome in the literature, extensively [1-3]. Similarly, sickle cell diseases (SCDs) are chronic destructive process mainly affecting capillaries. Hemoglobin S (Hb S) 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 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 spherocytosis. Loss of elasticity is probably present in whole life, but it is exaggerated with stressful conditions. The hard RBCs may take their normal elastic natures after normalization of the stresses, but they become hard bodies in time, permanently. The hard cells induced prolonged endothelial inflammation, edema, and fibrosis at capillaries, and tissue ischemia and infarcts are the terminal consequences [4,5]. On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution functions of them. We tried to understand whether or not there are some positive correlations between stroke and severity of SCDs.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and November 2014. All cases with SCDs were taken into the study. The SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Patients' 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. A checkup procedure including serum iron, total iron binding capacity, ferritin, creatinine,

hepatic 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 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 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 such patients [7]. An X-ray film 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% [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 hepatic function tests, ultrasonographic findings, and histologic procedure 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 [10,11]. Associated thalassemia minors are detected by serum iron, total iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. A stress electrocardiography is performed for cases with an abnormal electrocardiogram and/or angina pectoris. A 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 was diagnosed by the General Surgeons with the consultations in case of indication. Eventually, cases with stroke 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 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, p>0.05). Prevalences of associated thalassemia minors were also similar in them (73.3% versus 65.1%, respectively, p>0.05). As a different result, smoking was higher among the stroke cases (26.6% versus 13.0%, p<0.05) (Table 1).

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)			

Table 1: Characteristic features of the study cases.

The mean white blood cell (WBC) count, hematocrit (Hct) value, and the mean platelet (PLT) count of the peripheric blood were similar in both groups (p>0.05 for all) (Table 2).

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 2: Peripheric blood values of the study cases.

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).

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)
Digital clubbing	26.6% (8)	<0.001	7.9% (25)
Leg ulcers	26.6% (8)	<0.05	13.0% (41)
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

Table 3: Associated pathologies of the study cases.

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

It is obvious that atherosclerosis is the most common type of vasculitis all over the world, and it is the leading cause of morbidity and mortality particularly in elderlies. Probably whole afferent vasculatures including capillaries are affected 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 structures which can reduce the blood flow and increase BP further. In the SCDs, the hard RBCs induced chronic endothelial injury, inflammation, edema, and fibrosis mainly at the capillary level build up prototype of an advanced atherosclerosis even in younger ages.

SCDs are life-threatening genetic disorders affecting nearly 100.000 individuals in the United States [12]. They keep vascular endothelium mainly at the capillary level [13], since the capillary system is the main distributor of the hard RBCs to cells. Due to 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 on the vascular walls later in life. In other words, SCDs are mainly chronic inflammatory instead of obstructive disorders, and the major problem is probably endothelial injury, inflammation, edema, and fibrosis rather than the hard RBCs induced occlusions in the capillary lumen. As a result, the lifespans of females and males with the SCDs were 48 and 42 years in the literature [14], 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 much earlier in developed countries. On the other hand, the prolonged lifespan of females with SCDs and longer overall survival of females in the world cannot be explained by the atherosclerotic effects of smoking alone, instead it may be explained by more physical power requiring role of male sex in life [15,16].

Stroke is the third most common cause of death in Western countries, and thromboembolism due to atherosclerosis is the most common cause of the stroke. Similar to atherosclerosis, aging, male sex, smoking, DM, HT, dyslipidemia, and excess weight are the major accelerator factors of the stroke. Cerebral emboli usually come from atheromas in extracranial vessels or from thrombi in a damaged heart. Large atheromas usually affect the common carotid and vertebral arteries at their origins, but the cervical bifurcation of the common carotid artery is the most common site giving rise to emboli that cause stroke. Main trunk of the middle cerebral artery and its branches are the most common sites of intracranial thrombosis. Stroke is also a traumatic complication of the SCDs [17,18]. The incidence of stroke is

higher in sickle cell anemia (Hb SS) [19], and a higher WBC count is associated with a higher incidence [20]. It is attributed to sickling induced endothelial injury, WBC, PLT, and coagulation activation, hemolysis, and subsequent chronic endothelial inflammation, edema, remodeling, and fibrosis [21]. Probably, stroke is a complex and terminal event in the SCDs. All stroke episodes do not have a macrovascular origin, and disseminated capillary inflammation and endothelial edema may be important. Infections and other stressful conditions may precipitate the stroke, since the increased metabolic rate during such episodes may accelerate sickling, disseminated capillary injury, endothelial edema, and fibrosis. A preliminary result from the Multi-Institutional study of Hydroxyurea in the SCDs indicating a significant reduction of stroke in those on hydroxyurea [22] suggests that a significant proportion of strokes are secondary to the increased WBC and PLT counts induced disseminated capillary endothelial injury [13].

RBC transfusions are the most significant preventive approach for stroke in the SCDs [29,30]. They decrease sickle cell concentrations in blood, suppress their production in bone marrow, and prevent sickling induced endothelial injury, inflammation, edema, and fibrosis in brain, lungs, liver, bones, kidneys, and other organs [23,24]. Since the main pathology is disseminated and prolonged tissue ischemia in the SCDs [2], simple and repeated RBCs transfusions are highly effective to restore tissue oxygenation. Ileus is also a common pathology in the SCDs' patients probably due to their atherosclerotic natures [31], and all of the ileus cases were able to be treated with simple and repeated RBCs transfusions in the present study. But transfusions have to be given early in ileus and other clinically severe conditions rather than too late when the patient is clearly comatose. According to our experiences, simple and repeated RBC transfusions are superior to RBC exchange in the SCDs. First of all, simplicity of preparation of RBC suspensions in a short period of time provides advantages to clinicians. Secondly, preparation of one or two units of RBC suspension in each time rather than preparation of several units provides time to clinicians to prepare more units by preventing sudden death of such patients. Thirdly, transfusion of RBC suspensions in secondary health centers can prevent some deaths developed during transport to tertiary centers for exchange.

Painful crises are nearly pathognomonic for the SCDs, and they are precipitated by infection, operation, depression, and traumas. Although these painful crises are not life-threatening directly [25], crises induced increased metabolic rate may cause multiorgan failures on the chronic inflammatory background of the SCDs [26]. The severe pain is probably caused by the exaggerated inflammation of capillary endothelium all over the body, and the increased WBC and PLT counts and decreased Hct values even in silent periods may show the chronic inflammatory process during whole their lives in such cases. Similar to the present study, increased WBC counts even during the silent periods may be an independent predictor of severity [27], and it was associated with an increased risk of stroke by inducing disseminated capillary endothelial inflammation, edema, and fibrosis even in the brain [28]. According to our experiences, simple and repeated RBC transfusions according to the requirement are also effective during the severe painful crises both to relieve pain and to prevent sudden death which may develop secondary to the multiorgan failures on the chronic inflammatory background of the SCDs.

Two disease-modifying therapies, hydroxyurea daily and RBC transfusions in severe clinical conditions are underused [32]. Hydroxyurea is safe and highly effective for the SCDs [13]. It is an oral and cheap drug that 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) [33], its main action may be suppression of hyperproliferative WBCs and PLTs in the SCDs. Although presence of a continuous damage of hard RBCs on capillary endothelium, severity of the destructive process is probably exaggerated by the patients' own WBCs and PLTs. So mechanism of tissue destruction of the SCDs may mimic autoimmune disorders, and suppression of excessive proliferation of patients' own WBCs and PLTs by the drug may limit the capillary endothelial injury, inflammation, edema, and fibrosis induced disseminated 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 decrease severity of pain and tissue damage [34]. Furthermore, final Hb F levels did not differ with hydroxyurea therapy [34]. Due to the same reason, hydroxyurea is also used to suppress hyperproliferative cells in chronic myeloproliferative disorders and psoriasis, effectively. According to our practices during the eight-year period, the only side effect of hydroxyurea is a deep anemia. Although hydroxyurea increases Hct level in smaller doses, it may cause a deep anemia when used as a dose of 35 mg/kg/day. But this effect is usually harmless, and Hct level increases rapidly by decreasing the daily dose if the patient is clinically silent.

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

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