

Original Article

Tonsilectomy in sickle cell diseases

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Received December 13, 2014; Accepted February 3, 2015; Epub March 15, 2015; Published March 30, 2015

Abstract: Background: We tried to understand whether or not there are lowered prevalences of terminal consequences of sickle cell diseases (SCDs) with tonsilectomy. Methods: All cases with SCDs were taken into the study. Results: The study included 334 patients (164 females). There were 27 cases with tonsilectomy and 307 cases without. The mean ages, female ratios, and prevalences of associated thalassemia minors and smoking were similar in both groups ($P>0.05$ for all). Although the white blood cell and platelet counts of peripheral blood were higher in patients without tonsilectomy, the mean hematocrit value was lower in them, but the differences were nonsignificant probably due to the small sample size of the tonsilectomy group ($P>0.05$ for all). Similarly, although the painful crises per year, digital clubbing, leg ulcers, pulmonary hypertension, chronic obstructive pulmonary disease, rheumatic heart disease, avascular necrosis of bone, cirrhosis, stroke, and mortality were higher in cases without tonsilectomy, the differences were nonsignificant probably due to the same reason again ($P>0.05$ for all). Conclusion: There may be an inverse relationship between prevalence of tonsilectomy and severity of SCDs, and the tonsils may act as chronic inflammatory foci accelerating the chronic endothelial damage all over the body in such patients.

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

Introduction

Atherosclerosis may be the major cause of aging and mortality by means of disseminated tissue hypoxia in body. Cardiac cirrhosis in the background of the prolonged hepatic hypoxia may be a supporter pathology of the hypothesis. Whole afferent vasculature including capillaries are probably involved in the body. Some of the well known accelerators of the systemic process are physical inactivity, smoking, overweight, white coat hypertension, dyslipidemia, insulin resistance, and chronic inflammations for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), peripheral artery disease, chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), cirrhosis, coronary heart disease (CHD), osteoporosis, stroke, aging, and mortality [1-6]. Similarly, sickle cell diseases (SCDs) are chronic destructive process of endothelial cells all over the body [7]. 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 main problem, since sickling is rare in the peripheral 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 various stresses. 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 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 for the hard bodies. We tried to understand whether or not there are lowered prevalences of terminal consequences of SCDs with tonsilectomy.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between Ma-

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Table 1. Characteristic features of the study cases

Variables	Cases with tonsilectomy	P-value	Cases without tonsilectomy
Prevalence	8.0% (27)		91.9% (307)
Female ratio	51.8% (14)	Ns*	48.8% (150)
Mean age (year)	29.2 ± 10.0 (14-54)	Ns	29.6 ± 9.8 (5-59)
Thalassemia minors	51.8% (14)	Ns	66.7% (205)
Smoking	11.1% (3)	Ns	14.3% (44)

*Nonsignificant ($P>0.05$).

rch 2007 and August 2014. All patients with SCDs were studied. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Associated thalassemia minors are detected by serum iron, total iron binding capacity, ferritin, and the hemoglobin electrophoresis performed via HPLC. Their medical histories including painful crises per year, smoking habit, regular alcohol consumption, leg ulcers, stroke, and surgical operations were learnt. Cases with a history of one pack-year were accepted as smokers, and one drink a day for three years were accepted as drinkers. A check up procedure including serum creatinine value on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, 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 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. 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]. Avascular necrosis of bone was detected via MRI [10]. 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 liver biopsy in case of indication.

Digital clubbing is diagnosed with the ratio of distal phalangeal to interphalangeal diameters which is greater than 1.0, and with the presence of Schamroth's sign [11, 12]. A stress electrocardiography is performed in case

of an abnormal electrocardiogram 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. Eventually, the SCDs patients with tonsilectomy and without were collected into the two groups, and 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 334 patients with SCDs (164 females and 170 males). There were 27 cases with tonsilectomy and 307 cases without. The mean ages were similar in both groups (29.2 versus 29.6 years, respectively, $P>0.05$). Female ratios were also similar in them (51.8% versus 48.8%, respectively, $P>0.05$). Prevalences of associated thalassemia minors were similar in both groups, too (51.8% versus 66.7%, respectively, $P>0.05$). Prevalences of smoking were also similar in them (11.1% versus 14.3%, respectively, $P>0.05$) (**Table 1**). Although the white blood cell (WBC) and platelet (PLT) counts of peripheric blood were higher in patients without tonsilectomy, the mean hematocrit (Hct) value was lower in them (24.9% versus 23.6%), but the differences were nonsignificant probably due to the small sample size of the tonsilectomy group ($P>0.05$ for all) (**Table 2**). Similarly, although the painful crises per year, digital clubbing, leg ulcers, pulmonary hypertension, COPD, rheumatic heart disease, avascular necrosis of bone, cirrhosis, stroke, and mortality were higher in cases without tonsilectomy, the differences were nonsignificant probably due to the same reason again ($P>0.05$ for all) (**Table 3**). There were four

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Table 2. Peripheral blood values of the study cases

Variables	Cases with tonsilectomy	P-value	Cases without tonsilectomy
Mean WBC* counts (μL)	14.502 ± 4.655 (5.000-27.000)	Ns†	15.170 ± 6.654 (1.580-39.200)
Mean Hct‡ value (%)	24.9 ± 5.4 (13-39)	Ns	23.6 ± 4.9 (11-42)
Mean PLT§ counts (μL)	468.680 ± 139.002 (149.000-795.000)	Ns	481.140 ± 236.932 (48.800-1.827.000)

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

Table 3. Associated pathologies of the study cases

Variables	Cases with tonsilectomy	P-value	Cases without tonsilectomy
Painful crises per year	4.1 ± 7.1 (0-36)	Ns*	5.2 ± 8.2 (0-52)
Digital clubbing	0.0% (0)	Ns	10.4% (32)
Leg ulcers	3.7% (1)	Ns	15.6% (48)
Pulmonary hypertension	11.1% (3)	Ns	11.7% (36)
COPD†	11.1% (3)	Ns	13.3% (41)
CHD‡	11.1% (3)	Ns	6.1% (19)
CRD§	11.1% (3)	Ns	8.1% (25)
Rheumatic heart disease	3.7% (1)	Ns	7.1% (22)
Avascular necrosis of bone	14.8% (4)	Ns	21.8% (67)
Cirrhosis	0.0% (0)	Ns	4.8% (15)
Stroke	7.4% (2)	Ns	9.1% (28)
Mortality	0.0% (0)	Ns	5.2% (16)

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

patients with regular alcohol consumption who are not cirrhotic at the moment. Although anti-HCV was positive in seven of the cirrhotics, HCV RNA was detected as positive by polymerase chain reaction just in two.

Discussion

Capillary endothelial cells may mainly be damaged in the SCDs, 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 early years of life, but it may be difficult due to the severe loss of capillaries later in life. Finally, the mean lifespans were 42 years in males and 48 years in females in the literature [13], whereas they were 29.9 and 33.3 years in the present study, respectively. According to our experiences, the great differences may be secondary to delayed initiation of hydroxyurea treatment in our country [14]. On the other hand, the prolonged lifespan of females with SCDs and the longer overall survival of females in the world [15] can not be explained by atherosclerotic effects of smoking alone, instead it may be explained by physically dominant role of male sex in life [16].

Tonsillar hypertrophy is a common physical examination finding in the SCDs patients even during the silent periods, and it may be a result of relative immunosuppression in them, since sinusitis, pneumonia, osteomyelitis, rheumatic heart disease, and meningitis like infections are common in such patients. Tonsils are collections of lymphoid tissue facing into the aerodigestive tract. The set of lymphatic tissue known as Waldeyer's tonsillar ring includes the adenoid tonsil, two tubal tonsils, two palatine tonsils, and the lingual tonsil. When used unqualified, the term most commonly refers specifically to the palatine tonsils, which have non-keratinized stratified squamous epithelium, and are incompletely encapsulated. They are located at the sides of oropharynx between palatoglossal and palatopharyngeal arches. Tonsils are the largest in diameter in childhood, and they gradually undergo atrophy after puberty. These immunocompetent tissues are the immune system's first line of defense against ingested or inhaled foreign pathogens. Tonsils can become enlarged and inflamed and may need surgical removal. Tonsilectomy may be indicated if they obstruct the airway, interfere with swallowing, affect speech, or in case of recurrent tonsillitis. Similar to the spleen [17], the tonsils are probably found among the pri-

marily affected organs in the SCDs, and they may act as chronic inflammatory foci, and surgical removal may decrease secondary systemic inflammatory mediators and endothelial damage in such patients.

Painful crises are nearly pathognomonic symptoms of the SCDs, and they are precipitated by infection, operation, depression, or injuries. Although the crises are not thought to be life threatening directly [18], increased metabolic rate may terminate with multiorgan failures on the chronic inflammatory background of the diseases [19]. The severe pain is probably caused by the exaggerated inflammation of capillary endothelium, and the increased WBC and PLT counts and decreased Hct values show a chronic inflammatory process during whole their lives in such patients. Similar to the present study, increased WBC and PLT counts even during the silent periods were independent predictors of terminal consequences of the SCDs [20-22]. According to our practice, simple 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 preventive measure of stroke in such cases [23, 24]. Simplicity of preparation of RBC suspensions in a short period of time provides advantages to clinicians. Furthermore, preparation of one or two units of RBC suspension in each time provides time to clinicians to prepare more units by preventing sudden death. By this way, deaths developed during transport to tertiary health centers for RBC exchange can also be prevented.

Hydroxyurea is an oral, cheap, and effective drug for chronic myeloproliferative disorders and SCDs [14]. According to our experiences, it is a safe drug in the SCDs that may only cause anemia in high doses, and may increase hepatic function tests when used during crises. The dose is decreased in the first and the drug is withdrawn transiently in the second situations. Hydroxyurea prevents 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) [25], its primary action is probably suppression of hyperproliferative WBCs and PLTs in the SCDs. By this way, the chronic inflamma-

tory process of the SCDs that initiated at birth on the capillary endothelium can be suppressed with some extent. Due to the same action way, 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 WBCs and PLTs by hydroxyurea may limit the endothelial damage induced tissue ischemia and infarcts all over the body. Similarly, lower WBC counts were associated with lower crises rates and tissue damage in another study [26]. On the other hand, final Hb F levels did not differ in hydroxyurea users [26].

As a conclusion, there may be an inverse relationship between prevalence of tonsilectomy and severity of SCDs, and the tonsils may act as chronic inflammatory foci accelerating the chronic endothelial damage all over the body in such patients.

Disclosure of conflict of interest

None.

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