Digital clubbing may be a pioneer sign of cirrhosis in sickle cell patients

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ABSTRACT

Background: Sickle cell diseases (SCDs) are chronic destructive processes on endothelium initiating at birth all over the body. We tried to understand whether or not there is a relationship between digital clubbing and severity of SCDs.

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

Results: The study included 397 patients (193 females and 204 males). There were 36 patients (9.0%) with digital clubbing. The male ratio was significantly higher in the digital clubbing group (66.6% versus 49.8%, p<0.05). The mean age was significantly higher in the digital clubbing group too (36.5 versus 29.0 years, p=0.000). Similarly, smoking was also higher in the digital clubbing group, significantly (30.5% versus 11.0%, p<0.001). Beside that, prevalence of cirrhosis (25.0% versus 1.6%, p<0.001), leg ulcers (33.3% versus 11.9%, p<0.001), pulmonary hypertension (27.7% versus 9.6%, p<0.001), chronic obstructive pulmonary disease (38.8% versus 12.1%, p<0.001), coronary heart disease (27.7% versus 12.1%, p<0.01), and stroke (27.7% versus 6.9%, p<0.001) were all higher in the digital clubbing group, significantly. Although the mean white blood cell counts of peripheric blood were similar in both groups, the mean hematocrit value and platelet count were lower in the digital clubbing group, probably due to the effects of cirrhosis, significantly (p= 0.001 and p= 0.012, respectively).

Conclusion: The SCDs are chronic catastrophic processes on endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Digital clubbing may show an advanced disease and be a pioneer sign of cirrhosis in such patients.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis, digital clubbing, cirrhosis

Introduction

Chronic endothelial damage induced atherosclerosis may be the major cause of aging by causing disseminated tissue ischemia all over the body. For example, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in patients with pulmonary and/or cardiac diseases. Probably whole afferent vasculature including capillaries are involved in atherosclerosis. Some of the currently known accelerator factors of the inflammatory process are physical inactivity, overweight, and smoking for the development of irreversible end points including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were extensively researched under the issue of metabolic syndrome in the literature (1,2). Similarly, sickle cell diseases (SCDs) are chronic catastrophic processes on endothelium particularly at the capillary level. Hemoglobin S (HbS) causes loss of elasticity 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 very rare in the peripheric blood samples of the SCDs patients with associated thalassemia minors, and human survival is not so affected in hereditary elliptocytosis or spherocytosis. Loss of elasticity is probably present in whole lifespan, but exaggerated with increased metabolic rate of the body. The hard cells induced lifelong endothelial inflammation, edema, remodeling, and fibrosis mainly at the capillary level and terminate with generalized tissue hypoxia all over the body (3,4). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution function of them. We tried to understand whether or not there is a relationship between digital clubbing and severity of SCDs in the present study.

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and March 2015. All patients with the SCDs were studied. The SCDs are diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC) method. Medical histories including smoking habit, regular alcohol consumption, painful crises per year, surgical operations, priapism, leg ulcers, and stroke were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver 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 computed tomography of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (5). 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 is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia in the patients (6). An x-ray film of abdomen in upright position was taken just in patients 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 one second/forced vital capacity of less than 70% (7). Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent period is accepted as pulmonary hypertension (8). 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 period. Cirrhosis is diagnosed with liver 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 (9,10). Associated thalassemia minors are detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC method. Stress electrocardiography is just performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken 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 is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity of the abdomen. Eventually, cases with digital clubbing 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 397 patients with the SCDs (193 females and 204 males). There were 36 patients (9.0%) with digital clubbing. Mean age of patients was significantly higher in the digital clubbing group (36.5 versus 29.0 years, $p=0.000$). The male ratio was significantly higher in the clubbing group, too (66.6% versus 49.8%, $p<0.05$). Parallel to the male ratio, smoking was also higher in the digital clubbing group, significantly (30.5% versus 11.0%, $p<0.001$). Prevalences of associated thalassemia minors were similar in both groups (58.3% versus 66.2% in the clubbing group and other, respectively, $p>0.05$) (Table 1). On the other hand, prevalence of cirrhosis (25.0% versus 1.6%, $p<0.001$), leg ulcers (33.3% versus 11.9%, $p<0.001$), pulmonary hypertension (27.7% versus 9.6%, $p<0.001$), COPD (38.8% versus 12.1%, $p<0.001$), CHD (27.7% versus 12.1%, $p<0.01$), and stroke (27.7% versus 6.9%, $p<0.001$) were all higher in the digital clubbing group, significantly (Table 2). Although the mean white blood cell (WBC) counts of the peripheric blood were similar in both groups ($p<0.05$), the mean hematocrit (Hct) value and platelet (PLT) count of peripheric blood were lower in the digital clubbing group, probably due to the effects of cirrhosis, significantly ($p= 0.001$ and $p= 0.012$, respectively) (Table 3). There were 55 cases with leg ulcers, and 41 of them were male, so leg ulcers were much more common in males (20.0% in males versus 7.2% in females, $p<0.001$). Additionally,

Table 1: Characteristic features of the study cases

Variables	Cases with digital clubbing	*p*-value	Cases without digital clubbing
Prevalence	9.0% (36)		90.9% (361)
Male ratio	***66.6% (24)***	***<0.05***	***49.8% (180)***
Mean age (year)	***36.5 ± 10.9 (16-56)***	***0.000***	***29.0 ± 9.7 (5-59)***
Thalassemia minors	58.3% (21)	Ns*	66.2% (239)
Smoking	***30.5% (11)***	***<0.001***	***11.0% (40)***

*Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases

Variables	Cases with digital clubbing	*p*-value	Cases without digital clubbing
Painful crises per year	5.0 ± 9.1 (0-36)	Ns*	5.2 ± 8.1 (0-52)
Tonsilectomy	2.7% (1)	Ns	8.0% (29)
Priapism	2.7% (1)	Ns	2.7% (10)
Ileus	8.3% (3)	Ns	3.3% (12)
Cirrhosis	***25.0% (9)***	***<0.001***	***1.6% (6)***
Leg ulcers	***33.3% (12)***	***<0.001***	***11.9% (43)***
Pulmonary hypertension	***27.7% (10)***	***<0.001***	***9.6% (35)***
COPD†	***38.8% (14)***	***<0.001***	***12.1% (44)***
CHD‡	***27.7% (10)***	***<0.01***	***12.1% (44)***
CRD§	11.1% (4)	Ns	7.2% (26)
Rheumatic heart disease	5.5% (2)	Ns	6.0% (22)
Avascular necrosis of bones	13.8% (5)	Ns	22.9% (83)
ACS¶	8.3% (3)	Ns	3.3% (12)
Stroke	***27.7% (10)***	***<0.001***	***6.9% (25)***
Mortality	8.3% (3)	Ns	6.0% (22)

*Nonsignificant (p>0.05) †Chronic obstructive pulmonary disease ‡Coronary heart disease §Chronic renal disease Acute chest syndrome

Table 3: Peripheric blood values of the study cases

Variables	Cases with digital clubbing	*p*-value	Cases without digital clubbing
Mean WBC* counts (/µL)	15.329 ± 4.801 (7.000-26.600)	Ns†	15.114 ± 6.756 (1.580-48.500)
Mean Hct‡ values (%)	*21.0 ± 4.3 (12-32)*	*0.001*	*23.9 ± 5.1 (8-42)*
Mean PLT§ counts (/µL)	*378.916 ± 184.460 (114.000-1.142.000)*	*0.012*	*461.116 ± 231.611 (48.800-1.827.000)*

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

there were five patients with regular alcohol consumption who are not cirrhotic at the moment. Although antiHCV was positive in eight of the cirrhotics, HCV RNA was detected as positive just in two, by polymerase chain reaction method.

Discussion

Chronic endothelial damage induced atherosclerosis may be the most common type of vasculitis, and the leading cause of morbidity and mortality in the elderly. Probably whole afferent vasculature including capillaries are involved in the body. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent vessels are probably protected due to the much lower BP in them. Secondary to the prolonged endothelial damage and fibrosis, vascular walls become thickened; their lumens are narrowed, and they lose their elastic nature that can reduce the blood flow and increase BP further. Although early withdrawal of the causative factors including physical inactivity, excess weight, and smoking may prevent terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, the endothelial changes may not be reversed completely due to the fibrotic nature of them (11).

SCDs are life-threatening genetic disorders affecting nearly 100,000 individuals in the United States (12). As a difference from other causes of atherosclerosis, the SCDs probably keep vascular endothelium particularly at the capillary level (13), since the capillary system is the main distributor of the hard RBCs to tissues. The hard cells induced chronic endothelial damage, inflammation, edema, and fibrosis build up an advanced atherosclerosis in much younger ages of the patients. In other words, SCDs are mainly chronic inflammatory disorders, and probably the major problem is endothelial damage, inflammation, edema, and fibrosis induced occlusions in the vascular walls rather than the lumens all over the body. As a result, the lifespans of patients with the SCDs were 48 years in females and 42 years in males in the literature (14), whereas they were 33.0 and 30.0 years in the present study, respectively. The great differences may be secondary to delayed initiation of hydroxyurea therapy and inadequate RBC transfusions in emergencies in our country. On the other hand, longer lifespan of females with the SCDs (14) and longer overall survival of females in the world (15) 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 (16), since the physical power induced increased metabolic rate may terminate with an exaggerated sickling and atherosclerosis in body.

Digital changes may help to identify some systemic disorders in the body. For example, digital clubbing is a deformity of the finger and fingernails that has been known for centuries. It is characterized by loss of normal <165° angle between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (17). Schamroth's window test is a well-known test for the diagnosis of clubbing (10). The exact frequency of digital clubbing in the population is unknown, and some authors found clubbing in 0.9% of all patients admitted to the department of internal medicine (9), whereas the prevalence was 4.2% in both sexes in one of our studies (11). On the other hand, the exact underlying etiology of digital clubbing is unknown, but there are numerous theories about the issue, and chronic tissue hypoxia, vasodilation, secretion of growth factors, and some other mechanisms have been proposed (18-21). Moreover, the significance of diagnosing digital clubbing is not well established. For example, only 40% of digital clubbing cases turned out to have significant underlying diseases, while 60% had no medical problem on further investigations and remained well over the subsequent years (9). But digital clubbing is frequently associated with pulmonary, cardiac, and hepatic disorders that are featuring with chronic tissue hypoxia (9,11), since lungs, heart, and liver are closely related organs that affect their function in a short period of time. Similarly, hematologic disorders that are featuring with chronic tissue hypoxia may also terminate with digital clubbing. According to our observations, digital clubbing is probably an indicator of disseminated atherosclerosis particularly at the capillary level in the SCDs. For example, we observed clubbing in 9.0% of patients with the SCDs in the present study, and cirrhosis (25.0% versus 1.6%, p<0.001), leg ulcers (33.3% versus 11.9%, p<0.001), pulmonary hypertension (27.7% versus 9.6%, p<0.001), COPD (38.8% versus 12.1%, p<0.001), CHD (27.7% versus 12.1%, p<0.01), and stroke (27.7% versus 6.9%, p<0.001) like atherosclerotic end points were significantly higher among them. Similar to other studies, there was a male predominance in the clubbing group (66.6% versus 49.8%, p<0.05) that may also indicate role of smoking on clubbing (9,11).

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (11,22). Its atherosclerotic effects are

the most obvious in Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels and capillaries, and it has never been reported without smoking. COPD may also be a capillary endothelial inflammation terminating with disseminated pulmonary destruction, and it may be accepted as a localized Buerger's disease of the lungs. Although it has strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with weight loss (23). There may be an increased energy expenditure during smoking (24), and nicotine may decrease caloric intake in a dose-related manner after cessation of smoking (25). Nicotine may lengthen intermeal time, and decrease amount of meal eaten in animals (26). Body weight seems to be the highest in former, lowest in current, and medium in never smokers (27). Since smoking may also show the weakness of volition to control eating, prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of metabolic syndrome (28). Additionally, although CHD were detected with similar prevalences in both sexes (22), smoking and COPD were higher in males against the higher prevalences of body mass index and its consequences including dyslipidemia, HT, and DM in females.

Probably cirrhosis is also a systemic atherosclerotic process prominently affecting the hepatic vasculature, and aging, excess weight, smoking, alcohol consumption, infections, and other local or systemic inflammatory processes may be the major causes (29). The inflammatory process is enhanced with the release of various chemicals by lymphocytes to repair the damaged endothelium of hepatic vasculature (30), and the chronic inflammatory process terminates with an advanced atherosclerosis and tissue hypoxia in liver. Although cirrhosis is mainly thought to be an accelerated atherosclerotic process of the hepatic vasculature, there are close relationships between cirrhosis and digital clubbing, CHD, COPD, PAD, CRD, and stroke like other atherosclerotic end points (31). For example, most of the mortality cases in cirrhosis may actually be caused by cardiovascular diseases, and CHD may be the most common among them (32). Similarly, 25.0% of the digital clubbing cases were already cirrhotic, and the ratio was only 1.6% among the SCDs cases without clubbing in the present study ($p<0.001$). So beside the digital clubbing, CHD, COPD, leg ulcers, pulmonary hypertension, and stroke, cirrhosis may also be found among the terminal atherosclerotic end points of the SCDs (11,33).

Leg ulcers are seen in 10 to 20% of patients with the SCDs (34), and the ratio was 13.8% in the present study. The incidence increases with age and they are rare under the age of 10 years (34). Leg ulcers are also more common in males and sickle cell anemia (HbSS) cases (34). Similarly, there were 55 cases with leg ulcers, and 41 of them were male (20.0% in males versus 7.2% in females, $p<0.001$) in the present study. Additionally, mean ages of the patients with leg ulcers were significantly higher than the others (34.6 versus 28.7 years, $p<0.000$). They have an intractable nature, and around 97% of healed ulcers return in less than one year (35). The ulcers occur in distal areas with less collateral blood flow in the body (35). Chronic endothelial damage at the microcirculation due to the hard RBCs may be the major cause in the SCDs (34). Prolonged exposure to the causative factors due to the blood pooling in the lower extremities by the effect of gravity may also explain the leg but not arm ulcers in the SCDs. Probably the same mechanism is also true for diabetic ulcers, Buerger's disease, digital clubbing, varicose veins, and onychomycosis. Smoking may also have some additional roles for the ulcers (36), since both of them are much more common in males (34), and atherosclerotic effects of smoking are well-known (22). Venous insufficiency may also accelerate the process by causing pooling of causative hard RBCs in the legs. According to our eight-year experiences, prolonged resolution of ulcers with hydroxyurea therapy may also suggest that leg ulcers may actually be secondary to the increased WBC and PLT counts induced disseminated endothelial edema particularly at the capillary level.

Stroke is also a common complication of the SCDs (37), and thromboembolism in the background of accelerated atherosclerosis is the most common cause of it. Similar to the leg ulcers, stroke is higher in HbSS cases (38). Additionally, a higher WBC count is associated with a higher incidence of stroke (39). Sickling induced endothelial injury, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, remodeling, and fibrosis (40). Stroke in the SCDs may not have a macrovascular origin, instead disseminated endothelial edema may be much more important in the brain. Infections and other inflammatory processes may precipitate stroke, since increased metabolic rate may accelerate sickling and endothelial edema. Similar to the leg ulcers, a significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of strokes is secondary to the increased WBC and PLT counts' induced disseminated endothelial edema in the SCDs (13,41).

As a conclusion, SCDs are chronic catastrophic processes on endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Digital clubbing may show an advanced disease and be a pioneer sign of cirrhosis in such patients.

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