Atherosclerotic background of benign prostatic hyperplasia in sickle cell diseases

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ABSTRACT

Background: Sickle cell diseases (SCDs) are accelerated atherosclerotic processes. We tried to understand whether or not there is an atherosclerotic background of benign prostatic hyperplasia in the SCDs patients.

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

Results: The study included 428 patients (220 males). The mean ages were similar in males and females (30.6 versus 30.1 years, respectively, P>0.05). Smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were significantly higher in males (P<0.001 for both). 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 (7.7% 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, too. There were 11 males (5.0%) with lower urinary tract symptoms (LUTS) including urgency, weak stream, incomplete emptying, and nocturia with a mean age of 41.4 years. All patients could be treated with once daily 4 milligrams of doxazosin, orally.

Conclusion: SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Although the relatively younger mean age of the patients, LUTS are probably due to the disseminated endothelial damage, inflammation, edema, and fibrosis both in the arterial and venous systems of the prostate in the SCDs.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis, benign prostatic hyperplasia

Introduction

Chronic endothelial damage is the leading cause of aging, morbidity, and mortality by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are physical inactivity induced weight gain, smoking, alcohol consumption, and other chronic inflammatory processes including sickle cell diseases (SCDs), rheumatologic disorders, chronic infections, and cancers for the development of irreversible endpoints 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, morbidity, and mortality. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may prevent terminal endpoints, after development of obesity, HT, DM, cirrhosis, PAD, COPD, CRD, CAD, or stroke, endothelial changes can not be reversed completely due to their fibrotic natures (3). Benign prostatic hyperplasia (BPH) is also found among one of the most frequent health problems in men above the age of 50 years and its prevalence is progressively increased by aging. We tried to understand whether or not there is an atherosclerotic background of BPH in the SCDs patients in the present study.

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 were included into the study. The SCDs are diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking habit, regular alcohol consumption, painful crises per year, transfused units of red blood cells (RBCs) in their lives, surgical operations, leg ulcers, stroke, priapism, and lower urinary tract symptoms (LUTS) including urgency, weak stream, incomplete emptying, and nocturia 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 any other 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, liver 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 minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (4). 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 (5). 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 findings, laboratory parameters, 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 (6, 7). 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 bone is diagnosed by means of MRI (8). Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually male and female patients 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 428 patients with the SCDs (208 females and 220 males). Mean ages of the patients were similar in males and females (30.6 versus 30.1 years, respectively, P>0.05). Prevalence of associated thalassemia minors were similar in males and females, too (72.2% versus 67.7%, respectively, P>0.05). Smoking (24.0% versus 6.2%) and alcohol consumption (5.0% versus 0.4%) were significantly higher in males (P<0.001 for both) (Table 1). Transfused units of RBCs in their lives (47.6 versus 28.4, P=0.000), COPD (25.4% versus 7.2%, P<0.001), ileus (7.2% versus 1.4%, P<0.001), cirrhosis (7.7% 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, significantly. There were two cases with sickle cell retinopathy in males and two in females (0.9% versus 0.9%, P>0.05). There were 30 mortality cases (16 males) during the ten-year follow-up period.

Table 1: Characteristic features of the study cases

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: Associated pathologies of the study cases

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 RBC‡ units	*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	*7.7% (17)*	*<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	0.9% (2)
Mortality	7.2% (16)	Ns	6.7% (14)

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

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 2). On the other hand, there were 11 males (5.0%) with LUTS with a mean age of 41.4 ± 10.6 (27-58) years. All of the patients could be treated with once daily 4 milligrams of doxazosin, orally. Additionally, there were 22 cases (10.0%) with priapism with a mean age of 33.3 ± 8.1 (18-51) years.

Discussion

SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failure in early years of life. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of RBCs. Probably loss of elasticity instead of shape is the main problem since sickling is very rare in peripheric blood samples of cases with associated thalassemia minors, 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 chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated cellular hypoxia all over the body (9, 10). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (11, 12), since the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature (13), 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 RBC supports during severe medical or surgical events in Antakya region. Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCDs (14, 15). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling and sickling induced endothelial damage and inflammation all over the body. According to our ten-year observations, simple transfusions are superior to exchange. First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher gives time to clinicians to prepare more units by preventing sudden death of such individuals. Secondly, transfusion of one or two units of RBC suspensions in each time decreases the severity of pain and relaxes anxiety of the patients and their families in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions in each time will decrease transfusion-related complications in the future. Fourthly, transfusion of RBC suspensions in secondary health centers may prevent some deaths developed during transport to tertiary centers for the exchange. On the other hand, longer lifespan of females with the SCDs (13) and longer overall survival of females in general (16) cannot be explained by the atherosclerotic effects of smoking or alcohol alone, instead it may be explained by higher physical and emotional stresses of male sex that may terminate with an exaggerated atherosclerosis and sickling induced atherosclerosis all over the body (17).

BPH rather than hypertrophy is the most common benign neoplasm in men. Although prostate specific antigen (PSA) may be elevated in these patients because of increased organ volume and inflammation secondary to urinary tract infections, BPH does not lead to cancer. BPH involves hyperplasia of stromal and epithelial cells, terminating with the formation of large, commonly discrete nodules in the transition zone of the gland. When sufficiently large, the nodules apply pressure on the urethra and increase resistance to urinary flow. This is commonly felt as obstruction, although the urethral lumen is only compressed. Resistance to urinary flow requires the bladder to work stronger during voiding, possibly leading to progressive hypertrophy, instability, and atony of bladder muscle. BPH can be diagnosed by using the UWIN score (urgency, weak stream, incomplete emptying, and nocturia) (18). BPH may be caused by failure of the spermatic venous system resulting with increased hydrostatic pressure and testosterone levels, locally (19). Authors found that the one-way valves in the vertically oriented internal spermatic veins are destroyed in BPH patients causing elevated hydrostatic pressure up to 6-fold greater than the normal (19). The elevated pressure propagates to all interconnected vessels leading to a venous flow retrograde from higher pressure of the testicular veins to lower pressure of the prostate. They have found that free testosterone levels in this blood are elevated up to 130-fold above the serum (19). Consequently, the prostate is exposed both to an increased venous pressure that causes hypertrophy and to an elevated free testosterone level causing hyperplasia. On the other hand, an age-related impairment of blood supply to the gland may also have a key role in the development of BPH (20). An advanced atherosclerosis in elder men may cause chronic tissue hypoxia, and thus be a contributing factor in the pathogenesis (21). Smooth muscle proliferation may be an important and possibly androgen-dependent step in the development of atherosclerosis and BPH (22). Similarly, there was a larger prostate in men with type 2 DM (P=0.0058), HT (P=0.0317), obesity (P<0.0001), and low high density lipoprotein (HDL)-cholesterol (P=0.0132) and high insulin levels (P<0.0001) (23). The gland volume correlated positively with the systolic BP (P=0.03), obesity (P<0.0001), and fasting insulin (P<0.0001) and negatively with HDL-cholesterol levels (P=0.009) (23). As already known, they were significant components of the metabolic syndrome that is the accelerated atherosclerotic process all over the body (23). Similarly, frequency of CAD was 9% and 29% in men with PSA levels below and above 1.0 microgram/L, respectively (P<0.03) (22). These results may suggest that BPH may be one of the terminal endpoints of accelerated atherosclerotic process in the body.

Varices are abnormally dilated vessels with tortuous courses. They usually occur in the venous system of the legs. Related factors include pregnancy, obesity, menopause, aging, and heredity. In other words, varices are more frequent with female sex and components of the metabolic syndrome. Interestingly, although the younger mean ages of the patients (30.6 years in males and 30.1 years in females) in the present study and significantly lower body mass index (BMI) of the SCDs cases in the literature (4), deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs were higher among the study cases (8.6% in males and 5.7% in females, P>0.05). Normally, leg muscles pump veins to return blood to heart against gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination should be performed in upright position. Deep venous thrombosis is another possible cause of varicose veins. Severe long-standing varicose veins can lead to leg swelling, venous eczema, skin thickening, and ulcerations, but life-threatening complications are rare. Although the relatively younger mean age of the study cases and significantly lower BMI of the SCDs cases in the literature (4), the high prevalences of deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs (7.2%) may show an additional venous endothelial involvement in the SCDs.

Priapism is the painful erection of penis that does not return to its flaccid state within four hours in the absence of any stimulation (24). Damage to vascular endothelium may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, non-erectile penis (24). Ninety-five percent of clinically presented priapisms are veno-occlusive (low flow) type in which blood does not return adequately from the penis as in the SCDs. The other 5% are arterial (high flow) type usually caused by a blunt perineal trauma in which there is a short-circuit of the vascular system (24). Treatment of arterial type is not as urgent as that of venous type since there is no risk of ischemia (24). Oral pseudoephedrine or terbutaline may relax the stretched corporeal smooth muscles and increase permeability of erectile cavernous tissue that may permit easy flow of fluid from sinusoids into the venous system. If the drugs are not effective, aspiration of blood from the corpus cavernosum under local anesthesia is tried. If the aspiration also fails, distal shunts may cause the blood to leave the penis. Whereas in the SCDs, RBC support should be the treatment of choice in acute phase (25). RBC transfusions decrease sickle cell concentration in blood, suppress the bone marrow in production of abnormal RBCs, and eventually prevent further sickling induced damage to the penis. Whereas in chronic phase, hydroxyurea should be the treatment of choice in priapism in the SCDs. It is the only drug that was approved by Food and Drug Administration for the treatment of SCDs (11). It is an oral, cheap, safe, and highly effective drug for the SCDs that blocks cell division by suppressing formation of deoxyribonucleotides which are building blocks of DNA (12). Its main action may be suppression of hyperproliferative WBCs and PLTs in the SCDs (26). Although presence of continuous damage of hard RBCs particularly on capillary endothelium, severity of the destructive process is probably exaggerated by the patients' own WBCs and PLTs as in the autoimmune disorders. Similarly, lower neutrophil counts were associated with lower crises rates, and if a tissue infarct occurs, lower neutrophil counts may decrease severity of pain and tissue damage (27). According to our observations, hydroxyurea is an effective drug for prevention of attacks of priapism and its terminal consequences if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls later in life.

COPD is the third leading cause of mortality in the world (28). It is an inflammatory disorder mainly affecting the pulmonary vasculature, and physical inactivity induced weight gain, smoking, and aging may be the major causes. Probably regular alcohol consumption also takes a role in the inflammatory process. For example, both prevalence of alcohol consumption and COPD were significantly higher in males in the present study (P<0.001 for both). Similarly, COPD was one of the most frequent associated disorders in alcohol dependence in another study (29). Additionally, 30-day readmission rate to the hospitals was higher in COPD patients with alcoholism (30). Probably an accelerated atherosclerotic process is the main structural background of the COPD. The endothelial process is enhanced by release of various chemicals by inflammatory cells, and terminates with endothelial fibrosis and tissue losses in the lungs. Although COPD may mainly be thought as an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of a disseminated endothelial inflammation

all over the body, and close relationships were observed between COPD, CAD, PAD, and stroke (31, 32). Two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in smokers, and when the hospitalizations were researched, the most common causes were the cardiovascular diseases again (33). Similarly, 27% of mortalities were due to the cardiovascular causes in the moderate and severe COPD cases in another study (34). Due to the strong atherosclerotic natures of the SCDs and COPD, COPD may be one of the terminal endpoints of the SCDs due to the higher prevalences of priapism, leg ulcers, clubbing, CAD, CRD, and stroke in the COPD group in another study (35).

Smoking has major effects on systemic atherosclerotic processes including COPD, digital clubbing, cirrhosis, CRD, PAD, CAD, stroke, and cancers (36). Its atherosclerotic effects are the most obvious in COPD and Buerger's disease. Buerger's disease has never been reported in the absence of smoking in the literature. Smoking induced endothelial damage is probably seen in pulmonary vasculature much more than the other organs due to the higher concentrations of its products, here. But smoking may even cause cirrhosis, CRD, PAD, CAD, stroke, and cancers by the transport of its products within the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. On the other hand, beside the strong atherosclerotic effects, smoking in human beings and nicotine in animals may be associated with some weight loss (37). There may be increased energy expenditure during smoking (38), and nicotine may decrease caloric intake in a dose-related manner (39). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (40). Similarly, BMI seems to be the highest in the former and the lowest in the current smokers (41). As a pleasure in life, smoking may also show the weakness of volition to control eating. For example, prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (42). Additionally, although CAD was detected with similar prevalence in both sexes, smoking and COPD were higher in males against the higher prevalence of BMI and its terminal consequences including dyslipidemia, HT, and DM in females (36). Probably toxic substances of tobacco smoke cause a diffuse inflammation on vascular endothelium all over the body, and it is the major cause of loss of appetite during circulation of the substances within the blood, since the body can't eat anything during fighting. So regular smoking comes with a prominent weight loss in front of us, clinically. On the other hand, when we considered some antidepressant properties of smoking and alcohol, the higher prevalences of them may also show higher stresses and shortened survival in males.

Digital clubbing should alert physicians about some systemic disorders in the body (10). 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 (43). Some authors detected clubbing in 0.9% of all patients admitted to the department of internal medicine (7), whereas the prevalence was 4.2% in the same department in our university (10). The exact cause and significance is unknown but chronic tissue hypoxia has been proposed (44). In the above study, only 40% of clubbing cases turned out to have significant underlying

diseases while 60% remained well over the subsequent years (7). But according to our observations, digital clubbing is frequently associated with pulmonary, cardiac, and/or hepatic disorders or smoking that are featuring with chronic tissue hypoxia. As an explanation for that lungs, heart, and liver are closely related organs that affect their functions in a short period of time. Similarly, digital clubbing may be an indicator of disseminated atherosclerosis at the capillary level in the SCDs, and we observed clubbing in 10.2% of patients with the SCDs in the present study. Beside the effects of SCDs, the higher prevalences of smoking, COPD, and clubbing in males (P<0.001 for all) may also show some additional roles of smoking, COPD, and male sex on clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (45), and the ratio was 13.7% in the present study. Its incidence increases with age, male sex, and HbSS genotype (45). Similarly, its ratio was higher in males (20.0% versus 7.2%, P<0.001), and mean age of the patients with leg ulcers was higher than the others (35.1 versus 29.6 years, P<0.000), here. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (46). As an evidence of their atherosclerotic background, the leg ulcers occur in distal areas with less collateral blood flow in the body (46). The hard RBCs induced chronic endothelial damage at the capillary level may be the major cause in the SCDs (45). Prolonged exposure to the hard bodies due to blood pooling in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The hard RBCs induced venous insufficiencies may also accelerate the process by pooling of causative hard bodies in the legs, and vice versa. Pooling of blood in the lower extremities may also have some effects on the venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis. Beside the hard bodies, smoking and alcohol may also have some effects on the leg ulcers since both of them are more common in males, and their atherosclerotic effects are obvious in COPD, Buerger's disease, and cirrhosis (45). According to our ten-year observations, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to increased WBC and PLT counts induced prolonged endothelial inflammation and edema at the capillary level in the SCDs.

Stroke is also a common complication of the SCDs (47). Similar to acute chest syndrome (ACS) and leg ulcers, it is more common with the HbSS genotype and with a higher WBC count (26, 48). Sickling induced disseminated endothelial damage and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, and fibrosis in the brain (26). Stroke may not have a macrovascular origin, instead generalized endothelial inflammation and edema at the capillary level may be much more important in the SCDs. Infections, serious injuries, inflammatory disorders, and other stresses may precipitate the stroke since increased metabolic rate during such events may accelerate sickling and secondary endothelial inflammation and edema even in the brain. Similar to the ACS and leg ulcers, a significant reduction with hydroxyurea may also suggest that a significant proportion of stroke is secondary to increased WBC and PLT counts induced disseminated endothelial inflammation and edema in the brain in the SCDs (49).

As a conclusion, SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failure in early years of life. Although the relatively younger mean age of the patients, LUTS are probably due to the disseminated endothelial damage, inflammation, edema, and fibrosis both in the arterial and venous systems of the prostate in the SCDs.

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