Atherosclerotic background of hepatomegaly, left lobe hypertrophy, and cirrhosis in sickle cell diseases

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ABSTRACT

Background: We tried to understand whether or not there is an atherosclerotic background of hepatomegaly, left lobe hypertrophy, and cirrhosis in sickle cell diseases (SCDs).
Methods: All patients with the SCDs were included into the study.

Results: The study included 434 patients (222 males). Mean ages were similar in males and females (30.8 versus 30.3 years, respectively, P>0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were significantly higher in males (P<0.001 for both). Although the relatively younger mean ages, the prevalence of hepatomegaly (59.4%), left lobe hypertrophy (7.1%), cirrhosis (5.0%) were very high. On the other hand, transfused units of red blood cells in their lives (48.1 versus 28.5, P=0.000), chronic obstructive pulmonary disease (25.2% versus 7.0%, P<0.001), ileus (7.2% versus 1.4%, P<0.001), cirrhosis (8.1% versus 1.8%, P<0.001), leg ulcers (19.3% versus 7.0%, P<0.001), digital clubbing (14.8% versus 6.6%, P<0.001), coronary artery disease (18.0% versus 13.2%, P<0.05), chronic renal disease (9.9% versus 6.1%, P<0.05), and stroke (12.1% versus 7.5%, P<0.05) were all higher in males.

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 ages, the very high prevalence of hepatomegaly, left lobe hypertrophy, and cirrhosis are probably due to the disseminated endothelial damage, inflammation, and fibrosis both at the arterial and venous systems of the liver, and the left lobe hypertrophy may be a progression step between hepatomegaly and cirrhosis in the SCDs.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis, hepatomegaly, left lobe hypertrophy, cirrhosis
Introduction

Chronic endothelial damage may be the leading cause of aging-induced morbidities and mortalities 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 endothelial injuries. Therefore the term of veno-occlusive disease is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduce blood flow and increase systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are physical inactivity induced weight gain, smoking, alcohol, and other chronic inflammatory or infectious processes including sickle cell diseases (SCDs), rheumatologic disorders, tuberculosis, and cancers for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheral 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-induced morbidities and mortalities. They were discussed under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, after development of obesity, HT, DM, PAD, COPD, CRD, CAD, or stroke, the endothelial changes cannot be reversed completely due to their fibrotic nature (3). Similarly, cirrhosis is also a progressively increasing cause of morbidity and mortality in the world (4), and it may also be one of the terminal consequences of the systemic atherosclerotic process. We tried to understand whether or not there is an atherosclerotic background of hepatomegaly, left lobe hypertrophy, and cirrhosis in the SCDs.

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 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, alcohol, 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) in males 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 investigations, 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 were performed. Other bones were scanned for avascular necrosis according to the patients’ complaints. So avascular necrosis of bone was diagnosed by means of MRI (5). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (6). 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. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. 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 (8, 9). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken 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. Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually prevalences of hepatomegaly, left lobe hypertrophy, and cirrhosis were detected among all, and male and female patients with the SCDs were compared according to the terminal endpoints 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 434 patients with the SCDs (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, respectively, P=0.05). Prevalence of associated thalassemia minors were similar in males and females too, (72.5% versus 67.9%, respectively, P=0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were significantly higher in males (P<0.001 for both) ([Table 1]). Although the relatively younger mean ages of the patients, the prevalence of hepatomegaly (59.4%), left lobe hypertrophy (7.1%), and cirrhosis (5.0%) were very high ([Table 2]). On the other hand, transfused units of RBCs in their lives (48.1 versus 28.5, P=0.000), COPD (25.2% versus 7.0%, P=0.000), ileus (7.2% versus 1.4%, P=0.001), cirrhosis (8.1% versus 1.8%, P=0.001), leg ulcers (19.8% versus 7.0%, P=0.001), digital clubbing (14.8% versus 6.6%, P=0.001), CAD (18.0% versus 13.2%, P=0.05), CRD (9.9% versus 6.1%, P=0.05), and stroke (12.1% versus 7.5%, P=0.05) were all higher in males, significantly. There were 11 males (4.9%) with LUTS with a mean age of 41.5 ± 10.6 (27-58) years. All of the patients could be treated
with once daily 4 milligrams of doxazosin, orally. Additionally, there were 23 cases (10.3%) with priapism with a mean age of 33.4 ± 7.9 (18-51) years. There were two cases with sickle cell retinopathy in males and two in females (0.9% versus 0.9%, P>0.05). There were 31 mortality cases (17 males and 14 females) during the ten-year period. The mean ages of mortality were 30.2 ± 8.4 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (P>0.05) (Table 3).

Discussion

SCDs are chronic inflammatory processes on vascular endothelium terminating 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 pathology 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 infections, inflammation, and other stresses of the body. The hard RBCs induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated cellular hypoxia all over the body (10, 11). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (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 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 30.2 years in the present study, respectively. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea, and inadequate RBC supports during emergencies in Antakya region (14). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCDs (15). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow about the production of abnormal RBCs. So it decreases sickling-induced endothelial damage and inflammation all over the body.

Varices are abnormally dilated veins with tortuous courses, and they usually occur in the legs. Their related factors include pregnancy, obesity, menopause, aging, and heredity. In other words, varices are more common in females and in cases with metabolic syndrome. Normally, leg muscles pump veins to return blood against the 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. Deep venous thrombosis may also cause varicose veins. 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. Although the younger mean ages of the patients in the present study (30.8 years in males and 30.3 years in females) and significantly lower body mass index (BMI) of the SCDs cases in the literature (11), deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs were higher among the study cases (9.0% in males and 6.6% in females, P<0.05) indicating an additional venous endothelial involvement in the SCDs.

Both the frequency and complications of cirrhosis are increasing in the world. For instance, it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (4). Although the achieved development of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by aging of the human being and increased frequency of excess weight in the world. For instance, non-alcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even in children and adolescents at the moment (16, 17). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (16). NAFLD shares many features of the metabolic syndrome. Besides terminating with cirrhosis, NAFLD is associated with a higher overall mortality as well as with an increased prevalence of cardiovascular diseases (17). Authors have reported independent associations between NAFLD, impaired flow-mediated vasodilation, and increased carotid intima-media thickness (17, 18). NAFLD and cirrhosis may be considered as the hepatic consequences of the systemic accelerated atherosclerotic process, and hepatic fat is highly correlated with parameters of the metabolic syndrome (19). Probably smoking also takes a role in the endothelial inflammatory process in the liver, since the systemic inflammatory effects of smoking on endothelial cells is already known with Buerger’s disease and COPD (20). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic accelerated atherosclerotic process in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the higher concentrations of its metabolites in the liver. Similarly, aging alone may be another cause of systemic atherosclerotic process that prevents adequate tissue oxygenation. Chronic infectious or inflammatory diseases may also terminate with an accelerated atherosclerotic process (21). For example, chronic HCV infection had raised carotid intima-media thickness, and normalisation of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (21). Similarly, beside the COPD, ileus, leg ulcers, digital clubbing, CAD, CRD, and stroke, cirrhosis may also be one of the terminal endpoints of the SCDs.

COPD is the third leading cause of mortality in the world (22). It is an inflammatory disorder mainly affecting the pulmonary vasculature, and it may also be called cirrhosis of the lungs. Physical inactivity induced weight gain, smoking, and aging may be the major underlying causes. Probably alcohol also takes a role in the inflammatory process. For example, both prevalence of alcohol 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 (23). Additionally, 30-day re-admission rates were higher in COPD patients with alcoholism (24). Probably an accelerated atherosclerotic process is the main structural background of the COPD. The endothelial process is enhanced by release of various chemicals by inflam-
Table 1: Characteristic features of the study cases

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male patients with SCDs*</th>
<th>P-value</th>
<th>Female patients with SCDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>51.4% (220)</td>
<td>Ns†</td>
<td>48.5% (208)</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>30.6 ± 10.1 (5-58)</td>
<td>Ns</td>
<td>30.1 ± 9.9 (8-59)</td>
</tr>
<tr>
<td>Thalassemia minors</td>
<td>72.2% (159)</td>
<td>Ns</td>
<td>67.7% (141)</td>
</tr>
<tr>
<td>Smoking</td>
<td>24.0% (53)</td>
<td>&lt;0.001</td>
<td>6.2% (13)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>5.0% (11)</td>
<td>&lt;0.001</td>
<td>0.4% (1)</td>
</tr>
</tbody>
</table>

*Sickle cell diseases †Nonsignificant (P>0.05)

Table 2: Prevalences of hepatomegaly, left lobe hypertrophy, and cirrhosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hepatomegaly</th>
<th>P-value</th>
<th>Left lobe hypertrophy</th>
<th>P-value</th>
<th>Cirrhosis</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>59.6% (259)</td>
<td>7.1%</td>
<td>33.4 ± 10.7 (19-56)</td>
<td>5.0% (22)</td>
<td>37.0 ± 11.5 (19-56)</td>
<td>0.007</td>
</tr>
<tr>
<td>Male ratio</td>
<td>53.6% (139)</td>
<td>64.5%</td>
<td>33.4 ± 10.7 (19-56)</td>
<td>5.0% (22)</td>
<td>37.0 ± 11.5 (19-56)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean age</td>
<td>30.2 ± 9.5 (5-59)</td>
<td>Ns†</td>
<td>33.4 ± 10.7 (19-56)</td>
<td>5.0% (22)</td>
<td>37.0 ± 11.5 (19-56)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Sickle cell diseases †Nonsignificant (P>0.05)

Table 3: Associated pathologies of the study cases

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male patients with SCDs*</th>
<th>P-value</th>
<th>Female patients with SCDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful crises per year</td>
<td>5.0 ± 7.1 (0-36)</td>
<td>Ns†</td>
<td>4.9 ± 8.6 (0-52)</td>
</tr>
<tr>
<td>Transfused RBC# units</td>
<td>47.6 ± 61.6 (0-434)</td>
<td>0.000</td>
<td>28.4 ± 35.8 (0-206)</td>
</tr>
<tr>
<td>COPD§</td>
<td>25.4% (56)</td>
<td>&lt;0.001</td>
<td>7.2% (15)</td>
</tr>
<tr>
<td>Ileus</td>
<td>7.2% (16)</td>
<td>&lt;0.001</td>
<td>1.4% (3)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>7.7% (17)</td>
<td>&lt;0.001</td>
<td>1.9% (4)</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>20.0% (44)</td>
<td>&lt;0.001</td>
<td>7.2% (15)</td>
</tr>
<tr>
<td>Digital clubbing</td>
<td>14.0% (31)</td>
<td>&lt;0.001</td>
<td>6.2% (13)</td>
</tr>
<tr>
<td>CAD†</td>
<td>18.1% (40)</td>
<td>&lt;0.05</td>
<td>12.9% (27)</td>
</tr>
<tr>
<td>CRD**</td>
<td>10.4% (23)</td>
<td>&lt;0.05</td>
<td>6.2% (13)</td>
</tr>
<tr>
<td>Stroke</td>
<td>12.2% (27)</td>
<td>&lt;0.05</td>
<td>7.6% (16)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>12.7% (28)</td>
<td>Ns</td>
<td>12.5% (26)</td>
</tr>
<tr>
<td>Varices</td>
<td>8.6% (19)</td>
<td>Ns</td>
<td>5.7% (12)</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>6.8% (15)</td>
<td>Ns</td>
<td>5.7% (12)</td>
</tr>
<tr>
<td>Avascular necrosis of bones</td>
<td>25.0% (55)</td>
<td>Ns</td>
<td>25.0% (52)</td>
</tr>
<tr>
<td>Sickle cell retinopathy</td>
<td>0.9% (2)</td>
<td>Ns</td>
<td>0.9% (2)</td>
</tr>
<tr>
<td>Mortality</td>
<td>7.2% (16)</td>
<td>Ns</td>
<td>6.7% (14)</td>
</tr>
</tbody>
</table>

*Sickle cell diseases †Nonsignificant (P>0.05) ‡Red blood cell §Chronic obstructive pulmonary diseases Coronary artery disease **Chronic renal disease
matory cells, and terminates with endothelial fibrosis and tissue losses in the lungs. Although COPD may mainly be thought of 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 (25, 26). For instance, 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 (27). Similarly, 27% of mortalities were due to the cardiovascular causes in the moderate and severe COPD cases in another study (28). Due to the strong atherosclerotic background of COPD and SCDs, COPD may be one of the terminal endpoints of the SCDs (29).

Smoking has major effects on systemic atherosclerotic processes including COPD, digital clubbing, cirrhosis, CRD, PAD, CAD, stroke, and cancers (30). 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. On the other hand, beside the strong atherosclerotic effects, smoking in human beings and nicotine in animals may be associated with some weight loss (31). There may be an increased energy expenditure during smoking (32), and nicotine may decrease caloric intake in a dose-related manner (33). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (34). Similarly, BMI seems to be the highest in the former and the lowest in the current smokers (35). As a pleasure in life, smoking may also show the weakness of volition to control eating. For example, prevalence of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (36). Eventually, although CAD was detected with a similar prevalence in both sexes, smoking and COPD were higher in males against the higher prevalences of BMI and its terminal consequences including dyslipidemia, HT, and DM in females (30). Probably toxic substances of tobacco smoke cause a diffuse endothelial inflammation all over the body, and it is the major cause of loss of appetite during circulation of these substances within the blood, since the body doesn’t want to eat anything during fighting.

Digital clubbing is characterized by increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (37). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (38). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (9). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, and hepatic disorders as those are featuring with chronic tissue hypoxia. As an explanation for that, lungs, heart, and liver are closely related organs and those affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCDs and its prevalence was 10.8% in the present study. It may show chronic tissue hypoxia caused by disseminated endothelial inflammation at the capillary level in the SCDs. Beside the effects of SCDs, the higher prevalence 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 (39), and the ratio was 13.3% in the present study. Its incidence increases with age, male sex, and HbSS genotype (40). Similarly, its ratio was higher in males (19.8% versus 7.0%, P<0.001), and mean age of the patients with leg ulcers was higher than the others (35.3 versus 29.8 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 (39). As evidence of their atherosclerotic natures, the leg ulcers occur in distal areas with less collateral blood flow in the body (39). The hard RBCs induced chronic endothelial damage at the capillary level may be the major cause in the SCDs (40). 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 effects on the development of venous ulcers, diabetic ulcers, Buerger’s disease, digital clubbing, and onychomycosis. Beside the hard bodies, smoking and alcohol may also have effects on the leg ulcers since both of them are more common in males. Hydroxyurea is the only drug that was approved by the Food and Drug Administration for the treatment of SCDs (12). It is an oral, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (14). Its main action may be suppression of hyperproliferative white blood cells (WBCs) and platelets (PLTs) in the SCDs (41). Although presence of a continuous damage of hard RBCs on endothelium, severity of the destructive process is probably exaggerated by the patients’ own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (42). According to our ten-year experiences, 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 at the capillary level in the SCDs.

Stroke is also a common complication of the SCDs (43). Similar to acute chest syndrome (ACS) and leg ulcers, it is more common with the HbSS genotype and with a higher WBC count (41, 44). Sickling induced disseminated endothelial damage and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, and fibrosis in the brain (41). 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 (45).

As a 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 ages, the very high prevalences of hepatomegaly, left lobe hypertrophy, and cirrhosis are probably due to the disseminated endothelial damage, inflammation, and fibrosis both at the arterial and venous systems of the liver, and the left lobe hypertrophy may be a progression step between hepatomegaly and cirrhosis in the SCDS.

References