What a low prevalence of malignancies in sickle cell diseases

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Abstract

Background: We tried to understand whether or not there is a lower prevalence of malignancies due to chronic vascular endothelial inflammation in the sickle cell diseases (SCDs).

Methods: All patients with the SCDs and age and sex-matched controls were studied.

Results: The study included 428 patients with the SCDs (220 males) and 518 controls (266 males). Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, p>0.05). Both smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were higher in males with the SCDs (p<0.001 for both). Although various malignancies were diagnosed in 11.5% of the control cases (23 females and 37 males), this ratio was only 0.4% (one female and one male) in the SCDs (p<0.001). On the other hand, 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 (7.2% 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 with the SCDs.

Conclusion: SCDs are chronic and severe inflammatory processes on vascular endothelium initiated at birth, and terminate with end-organ insufficiencies in early years of life. Such permanent inflammatory processes may increase clearance of malignant cells by the immune system and that may be the cause of significantly lower prevalence of malignancies in the SCDs.

Key words: Chronic vascular endothelial inflammation, sickle cell diseases, malignancies, immunologic activation

Introduction

Chronic endothelial damage may be the major cause of aging and associated morbidity and mortalities by causing disseminated tissue hypoxia all over the body. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause, and probably whole afferent vasculature including capillaries are involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, excess weight, smoking, and alcohol for the development of irreversible consequences 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 and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Similarly, sickle cell diseases (SCDs) are severe and permanent inflammatory processes on vascular endothelium initiated at birth, and terminate with end-organ insufficiencies in early years of life. Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the major problem since sickling is rare in peripheric blood samples of the SCDs 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 severe and permanent vascular endothelial inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (3, 4). Capillary systems may mainly be involved in the process due to their distribution function for the hard bodies. We tried to understand whether or not there is a significantly lower prevalence of malignancies due to the permanent vascular endothelial inflammation in the SCDs.

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 and age and sex-matched controls were studied. The SCDs were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories of SCDs patients including smoking habit, regular alcohol consumption, painful crises per year, transfused units of RBCs in their lives, surgical operations, leg ulcers and stroke, 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. The SCDs with acute painful crisis were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including erythrocyte sedimentation rate, C-reactive protein, serum total protein and albumin, serum iron, iron binding capacity, ferritin, creatinine, hepatic function tests, markers of hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), 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 for avascular necrosis were scanned according to the patients' complaints. Additional diagnostic methods including thoracic and abdominopelvic computed tomographies (CT), endoscopy, bronchoscopy, colonoscopy, tissue sample biopsies including bone marrow biopsies, and flow cytometric studies were performed according to the requirements in suspected cases of malignancies, and malignancies were diagnosed, histopathologically. 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% (5). 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 (6). 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, liver function tests, ultrasonographic evaluation, and tissue samples in case of requirement. 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 (7, 8). 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 bones is diagnosed by means of MRI (9). Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, prevalence of various malignancies were detected both in the SCDs and control 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 (220 males) and 518 controls (266 males), totally. Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, p>0.05). Mean ages of the control cases were 30.8 versus 30.5 years, respectively (p>0.05 for both). Prevalence of associated thalassemia minors were similar in males and females with the SCDs (72.2% versus 67.7%, respectively, p>0.05). Both smoking (24.0% versus 6.2%) and alcohol consumption (5.0% versus 0.4%) were significantly higher in males with the SCDs (p<0.001 for both) (Table 1).

Table 1: Characteristic features of the sickle cell patients

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)

Although various malignancies were diagnosed in 11.5% of the control cases (23 females and 37 males), this ratio was only 0.4% (one female and one male) in the SCDs group (p<0.001) (Table 2).

Table 2: Comparison of the patients and control groups

Variables	Patients with SCDs*	*p*-value	Control cases
Number	428	Ns†	518
Female ratio	48.5% (208)	Ns	48.6% (252)
Mean age of males	30.6 ± 10.1 (5-58)	Ns	30.8 ± 10.2 (9-59)
Mean age of females	30.1 ± 9.9 (8-59)	Ns	30.5 ± 9.8 (10-58)
Prevalence of malignancies	***0.4% (2)***	***<0.001***	***11.5% (60)***

*Sickle cell diseases †Nonsignificant (p>0.05)

There were nine patients with Hodgkin's lymphoma, six with acute lymphoblastic leukemia, five with acute myelogenous leukemia, five with Ph-positive chronic myelocytic leukemia, four with CD20-positive diffuse large B-cell lymphoma, four with sarcoma (Ewing's sarcoma, liposarcoma, soft tissue sarcoma, and osteosarcoma), three with ovarian cancer, three with breast cancer, three with colorectal cancer, three with lung cancer (two non-small cell and one small cell carcinomas), two with follicular lymphoma, two with chronic lymphocytic leukemia, two with multiple myeloma, two with T-cell lymphoma, one with medulloblastoma, one with stomach cancer, one with hepatocellular carcinoma (HCC) in the presence of hepatitis B surface antigen (HBsAg) positivity, one with Burkitt's lymphoma, one with primary peritoneal carcinomatosis, one with testicular cancer, and one with malignant epithelial tumor in the control group. Whereas there was just a breast cancer in a female and a non-small cell carcinoma of lung in a male with the SCDs (p<0.001 both for females and males). On the other hand, transfused RBC units in their lives (47.6 versus 28.4 units, p=0.000), COPD (25.4% versus 7.2%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (7.2% 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 with the SCDs, significantly. There were two cases with sickle cell retinopathy in males and one in females (p>0.05). There were 30 mortality cases (16 males) during the ten-year follow-up period. 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 3 - next page). Beside these, there were four patients with HBsAg positivity (0.9%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR) method. Although antiHCV was positive in 5.8% (25) of the study cases, HCV RNA was detected as positive just in three (0.7%) by PCR.

Table 3: Associated pathologies of the sickle cell patients

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 units of RBCs‡	***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	***7.2% (16)***	***<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	0.4% (1)
Mortality	7.2% (16)	Ns	6.7% (14)

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

Discussion

Chronic endothelial damage may be the leading cause of early aging and premature death in human beings. Physical inactivity, excess weight, smoking, alcohol, chronic inflammatory or infectious processes, and cancers may accelerate the process. Probably, it is the most common type of vasculitis all over the world. Whole afferent vasculature including capillaries may mainly be involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the permanent endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature that reduces blood flow and increases systolic BP further. Although early withdrawal of the causative factors may retard the final consequences, after development of HT, DM, cirrhosis, COPD, CRD, CAD, PAD, mesenteric ischemia, osteoporosis, or stroke, endothelial changes cannot be reversed completely due to their fibrotic natures (10).

SCDs are life-threatening hereditary disorders affecting around 100,000 individuals in the United States (11). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (12), because the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced severe and permanent endothelial damage, inflammation, edema, and fibrosis terminate with end-organ insufficiencies in early years of life. 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 medical or surgical emergencies in Hatay region of Turkey. Actually, RBC supports must be given during all medical or surgical emergencies in which there is an evidence of clinical deterioration in the SCDs (14, 15). RBC supports decrease sickle cell concentration in the circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling induced endothelial damage all over the body during such events. According to our 18-year experiences, simple RBC transfusions are superior to the exchange. First of all, preparation of one or two units of RBC suspensions at each time rather than preparation of six units or higher provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusion of one or two units of RBC suspensions at each time decreases the severity of pain and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions at each time decrease transfusion-related complications in the future. Fourthly, transfusions of RBC suspensions in the secondary health centers prevent some deaths developed during transport to the tertiary centers for the exchange. Fifthly, transfusions of RBC suspensions in the secondary health centers save some extra costs on the health system incurred during the transport to tertiary centers. On the other hand, longer survival of females in the SCDs (13) and longer overall survival of females in the world (16) cannot be explained by the atherosclerotic effects of smoking and alcohol alone, instead it may be explained by the physical power dependent role of male sex in life that may terminate with an exaggerated sickling and vascular endothelial damage in early years of life (17).

Malignancy is a proliferation of cell with loss of normal controls resulting in unregulated growth, lack of differentiation, local tissue invasion, and metastasis. Although the genetic background of this unregulated cell growth cannot be detected in all cancer types, yet it is highly suspected that this abnormal behavior is caused by a DNA change in the cancer cell since the cell behaves under the control of its genetic material. Mutations of genes are responsible for the excessive proliferation of the malignant cells. These mutations may alter the quantity or behavior of the proteins encoded by growth-regulating genes and accelerate cell division. Oncogenes are abnormal genes that normally regulate cell growth. For instance, the ras gene is abnormal in about 25% of all human cancers (18). Ras protein is encoded by the ras gene, and it signals cancer cells to divide. Another example of the oncogenic activity is protein kinases that are the enzymes regulating several cellular activities. Many cancers contain structurally altered protein kinases. If overproduced or altered, these kinases stimulate cell division, continuously. Tumor suppressor genes normally suppress the development of cancers by encoding proteins. Mutations in the tumor suppressor genes occur in many cancers, allowing affected cells to divide, continuously (19). Another important regulatory protein, p53, prevents replication of damaged DNA, and promotes apoptosis of the cells. Inactive or altered p53 allows cells with abnormal DNA to survive and divide. The p53 gene appears defective in most of the human malignancies (20). The deletion, translocation, or duplication of important genes provides proliferative advantages to cancer cells over the normal cells, and a tumor may develop. Similarly, chromosomes break easily, putting children at high risk of developing cancers in some congenital diseases (21). Viruses can also cause cancers in human beings by integration of the provirus (double-stranded DNA copy of the viral RNA genome) into the cellular genome. For example, HBV accounts for more than 60% of HCC cases (22). Similarly, we detected a case of HCC in the presence of HBsAg positivity in the control group in the present study. Ultraviolet radiation and ionizing radiation are also carcinogenic by means of the DNA damage; for example, survivors of the atomic bomb in Hiroshima and Nagasaki had higher prevalence of several cancers (23). Similarly, when ionizing radiation in the form of x-rays is used to treat nonmalignant diseases including acne and ankylosing spondylitis, prevalence of several cancers increase. Normally, cancers cells with abnormal genetic material may develop in the human body everyday but immune cells, particularly the natural killers, detect and destroy them. The increased prevalence of several types of human cancers with aging may also show the significance of the immune system for the cancer development. The weakened immunity by aging may increase prevalence of cancers and reactivation tuberculosis in the human being (24). Disseminated atherosclerotic process all over the body by aging may also be important for the weakened immunity since immune cells cannot reach end organs of the body (25). So cancer cells proliferate easily since they have some survival advantages over the normal cells secondary to the genetic changes. On the other hand, immunologic activation may be important for the clearance of cancer cells in the body. Similarly, chronic vascular endothelial inflammation of the SCDs initiated at birth may increase clearance of the abnormal cells by the body's own immune cells and decrease prevalence of the malignancies in such patients. The prevalence of malignancies were significantly lower in the SCDs in the present study ($p<0.001$ both for females and males). On the other hand, a strong immune system is also important for the prevention of malignancies since immune cells can destroy the genetically changed cells. For example, patients with immunodeficiency including HIV infection and aging are at higher risk for various cancers. Patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or Sjögren's syndrome are at higher risk for lymphoma, usually the B-cell type, presumably due to the altered immunologic status of the patients. Similarly, parallel to the lower prevalence of malignancies, we detected significantly lower prevalence of SLE and RA in the SCDs in the previous studies (26, 27).

SCDs are severe inflammatory processes terminating with major health problems in early years of life (28). For example, menarche is retarded in females with the SCDs (4). Additionally, the severe and permanent vascular endothelial inflammation all over the body causes an overlapping chronic disease anemia (29). Furthermore, end-organ insufficiencies can even suppress the immune system of the patients. Sinusitis, tonsillitis, and urinary tract infections are the common causes of painful crises and hospitalizations, and they can rapidly progress into the severe and life-threatening infections including pneumonia, meningitis, and sepsis due to the relative immunosuppression in the SCDs (30). For example, prolonged tonsillary hypertrophy is a common physical examination finding that may be the result of a prolonged infectious process due to the relative immunosuppression in them (31). Severe and permanent endothelial inflammation induced prominent weight loss and cachexia are also common in them (4). Autosplenectomy, painful crises, hospitalizations, invasive procedures, RBC supports, medications, prevented normal daily activities, and an eventually suppressed mood of the body can even suppress the immune system (32, 33). In another definition, SCDs may cause a moderate immunosuppression with several mechanisms in the human body. Although the moderate to severe immunosuppression, the significantly lower prevalence of malignancies in the SCDs may be explained by the permanently activated immune cells on vascular endothelium since such immune cells increase clearance of genetically changed malignant cells all over the body.

As a conclusion, SCDs are chronic and severe inflammatory processes on vascular endothelium initiated at birth, and terminate with end-organ insufficiencies in early years of life. Such permanent inflammatory processes may increase clearance of malignant cells by immune system all over the body which may be the cause of significantly lower prevalence of malignancies in the SCDs.

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