What a low prevalence of autoimmune thyroiditis in sickle cell diseases

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Abstract

Background: We tried to understand whether or not there is a chronic inflammatory background of autoimmune thyroiditis (AT) on vascular endothelium in 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 414 controls (213 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 significantly higher in males with the SCDs (p<0.001 for both). Although AT was diagnosed in 7.2% of the control cases (26 females and 4 males), this ratio was only 0.7% (just in 3 males) in the SCDs patients (p<0.001). On the other hand, transfused red blood cell units 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 severe inflammatory processes on vascular endothelium at the capillary level, terminating with an accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms that may be the cause of significantly reduced prevalence of AT in SCDs.

Key words: Autoimmune thyroiditis, sickle cell diseases, chronic endothelial damage, atherosclerosis

Introduction

Chronic endothelial damage may be the major cause of aging and related 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 induced 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 premature aging and death. They were researched under the title of metabolic syndrome in the literature (1, 2). Similarly, sickle cell diseases (SCDs) are chronic inflammatory processes on vascular endothelium at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the main problem because 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 life, but exaggerated with increased metabolic rate of the body. The hard RBCs induced chronic endothelial inflammation, edema, and fibrosis at the capillary level 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 chronic inflammatory background of autoimmune thyroiditis (AT) on vascular endothelium at the capillary level 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 with them were included into the study. The SCDs were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories of the SCDs patients including smoking habit, regular alcohol consumption, painful crises per year, transfused RBC units 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. Cases with acute painful crisis or another 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, thyroid 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. Thyroid autoantibodies including thyroid peroxidase autoantibodies (TPOAb) and antithyroglobulin antibodies (TgAb) were studied just in cases with an abnormal thyrotrophin (TSH) concentration in serum, and AT was diagnosed by the positivity or positivities of the thyroidal autoantibodies together with an abnormal TSH concentration in serum. ELISA (The Trinity Biotech Captia) was used to detect the serum positivities of the TPOAb and TgAb. 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 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 (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 computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, prevalence of AT was detected both in the SCDs patients and in the controls, 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 208 females) and 414 age and sex-matched control cases (213 males and 201 females), 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 30.6 versus 30.3 years in males and females, 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 (5.0% versus 0.4%) were significantly higher in males with the SCDs (p<0.001 for both) (Table 1). Although AT was diagnosed in 7.2% of the control cases (26 females and 4 males), this ratio was only 0.7% (just in 3 males) in the SCDs patients (p<0.001) (Table 2). The mean ages of AT were 33.4 ± 10.9 (17-56) and 38.0 ± 20.0 (18-58) years in the control and SCDs groups, respectively (p>0.05). On the other hand, transfused RBC units 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 (7.2% 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). 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.

Discussion

Chronic endothelial damage, as the most common type of vasculitis, may be the leading cause of premature aging and related morbidity and mortalities in human beings. Physical inactivity induced excess weight, smoking, alcohol, chronic inflammatory and infectious processes, and cancers may accelerate the process. Probably whole afferent vasculature including capillaries are mainly 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 chronic endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature and reduce blood flow and increase systolic BP further. Although early withdrawal of causative factors may retard final consequences, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed completely due to their fibrotic nature (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 at the capillary level mainly (12), since the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial damage, inflammation, edema, and fibrosis build 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 of the diseases, delayed initiation of hydroxyurea therapy, and inadequate RBC support during severe medical and surgical events in Antakya region. Actually, RBC supports must be given during all medical and surgical events in which there is 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 ten-year experiences, simple RBC transfusions are superior to 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 families in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions at each time will decrease transfusion-related complications in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers prevents some deaths developed during transport to the tertiary centers for the exchange. On the other hand, longer survival of females in the SCDs (13) and longer overall survival of females in the world cannot be explained by the atherosclerotic effects of smoking and alcohol alone, instead it may be explained by higher physical and emotional stresses of male sex in life that may terminate with an exaggerated sickling and atherosclerotic process in early years of life (16, 17).

AT is an organ specific disease, characterized by lymphocytic infiltration of the gland and production of autoantibodies, directed against thyroid specific antigens (18). Iatrogenic destruction of the gland and AT represent the most common causes of adult hypothyroidism in iodine-sufficient areas (19). It is subdivided into Hashimoto's thyroiditis (chronic lymphocytic thyroiditis), Graves' disease, and painless thyroiditis, which is also called postpartum thyroiditis if it develops after birth. These subtypes may convert to each other over time. Patients may come with hypo- or hyperthyroidism and/or goiter, especially with the micronodulation (20). AT accounts for 40% of goiter cases in young adults (21). Ophthalmopathy is more common with Graves' form of the disease. Presence of TPOAb and/or TgAb together with an abnormal TSH concentration in serum is usually enough for the diagnosis. AT mainly affects middle age and elder females, therefore an abnormal TSH

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)

Table 2: Comparison of the patients and control groups

Variables	Patients with SCDs*	*p*-value	Control cases
Number	428	Ns†	414
Female ratio	48.5% (208)	Ns	48.5% (201)
Mean age of males	30.6 ± 10.1 (5-58)	Ns	30.6 ± 10.9 (11-55)
Mean age of females	30.1 ± 9.9 (8-59)	Ns	30.3 ± 10.3 (12-56)
Prevalence of AT‡	***0.7% (3)***	***<0.001***	***7.2% (30)***

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Autoimmune thyroiditis

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 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	***7.2% (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 cell §Chronic obstructive pulmonary diseases ¶Coronary artery disease **Chronic renal disease

concentration in serum is usually accepted as a proof of AT in iodine-sufficient areas (22). Autopsy studies, performed in England and USA, have shown that various degrees of thyroiditis are present in 40-45% of females and 20% of males (23). Prevalence of the two autoantibodies may reach up to 33% in females older than 70 years of age (24). It is believed that autoimmune procedure of AT is initiated by the activation of thyroid antigens specific CD4 (+) T lymphocytes (T-helpers). Although the antigen specific T-helpers could be isolated in thyroid tissues of Graves' patients, they couldn't be detected in Hashimoto's thyroiditis (25). Activation mechanism of T-helpers is still unknown. Currently two hypotheses are thought concerning this activation mechanism. According to the first hypothesis, infections by some viruses or bacteria, carrying proteins similar to the thyroidal ones, may activate the thyroid specific T-helpers. This way is dependent upon the fact of molecular similarity. Representation of intracellular proteins to T-helpers by thyroid epithelial cells is the second hypothesis. This hypothesis is also supported by the fact that although thyroidal cells of AT patients represent major histocompatibility complex-class II (MHC-class II) proteins (HLA-DR, HLA-DP ve HLA-DQ), normal thyroidal cells don't represent them (26). These proteins are required for

representation of antigens to T-helpers. Once activated, self-reactive T-helpers may cause production of thyroidal antibodies by stimulating autoreactive B lymphocytes. Until now three antigenic targets have been detected on the thyroid. They are thyroglobulin (storage protein of thyroid hormones), thyroid microsomal antigen (thyroid peroxidase enzyme as the rate-limiting step of thyroidal hormone synthesis), and receptor of TSH. Some other antigenic structures of the thyroid and some other thyroid growth initiating immunoglobulins other than the TSH receptor stimulating ones have been mentioned and are highly suspected but they couldn't be demonstrated up to now (27). Similarly, we observed that 86.6% of cases with AT were females with a mean age of 32.5 years in the control group in the present study. So AT is a nearly seven times more frequent disease in females. Whereas we detected just three patients with AT in the SCDs patients, and all of them were males with a mean age of 38.0 years. In other words, we were not able to detect any female patient with AT in the SCDs group, and the prevalence of AT was significantly lower in the SCDs than the age and sex-matched controls with unknown mechanisms, yet (0.7% versus 7.2%, p<0.001).

SCDs are severe inflammatory processes terminating with significant health problems in both genders (28). For example, menarche is significantly retarded in females with the SCDs (29). Additionally, the severe chronic inflammation all over the body causes an overlapping chronic disease anemia. Furthermore, end-organ insufficiencies can even suppress the immune system of the patients. Acute sinusitis, tonsillitis, and urinary tract infections are the common causes of acute painful crises and hospitalizations, and they can easily progress into the severe and life-threatening infections including pneumonia, meningitis, and sepsis due to the relative immunodeficiency in such patients (30). Tonsillary hypertrophy is a frequent physical examination finding that may be a result of a prolonged infectious process due to the relative immunodeficiency of the patients (31). Severe and prolonged endothelial inflammation induced prominent weight loss and cachexia are also common in them (4). Autosplenectomy, recurrent painful crises, frequent hospitalizations, invasive procedures, red blood cell supports, medications, prevented normal daily physical activities, and an eventually suppressed mood of the body can even suppress the normal immune system of the body (32, 33). In another definition, SCDs may cause moderate to severe immunosuppression in the human body that may be the cause of significantly reduced prevalence of AT in the SCDs in the present study.

As a conclusion, SCDs are severe inflammatory processes on vascular endothelium at the capillary level, terminating with accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms in the human body that may be the cause of significantly reduced prevalence of AT in the SCDs.

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