What a low prevalence of rheumatoid arthritis in sickle cell diseases

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Abstract

Background: We tried to understand whether or not there is a lower prevalence of rheumatoid arthritis (RA) due to moderate to severe immunosuppression 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 433 controls (223 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 RA was diagnosed in 2.7% of the control cases (six females and six males), this ratio was only 0.2% (just one female) in the SCDs patients (p<0.01). 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 and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failures in early years of life. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms that may be the cause of significantly lower prevalence of RA in the SCDs.

Key words: Rheumatoid arthritis,
sickle cell diseases, chronic endothelial damage, immunosuppression

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 premature aging and death. They were researched under the title of metabolic syndrome in the literature (1, 2). Similarly, sickle cell diseases (SCDs) are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with 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 since sickling is rare in peripheric blood samples of the SCDs 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 severe and continuous 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 lower prevalence of rheumatoid arthritis (RA) because of moderate to severe immunosuppression 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. 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, hepatic 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. Patients with RA were classified with the criteria of early rheumatoid arthritis (ERA) (5). The ERA criteria include a morning stiffness of 30 minutes or longer, arthritis of three or more joint areas, arthritis of hand joints, positivity of rheumatoid factor (RF), and positivity of anti-cyclic citrullinated peptide (anti-CCP) antibody. RA is defined by the presence of three or more of the criteria. In differential diagnosis, systemic lupus erythematosus (SLE) is classified with the American College of Rheumatology criteria of 1997 (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. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (8). 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 (9, 10). 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 (11). 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 RA were detected both in the SCDs and control groups. 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 433 age and sex-matched control cases (223 males and 210 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 30.4 versus 30.3 years in males and females, respectively (p>0.05 for both). Prevalences 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). Although RA was diagnosed in 2.7% of the control cases (six females and six males), this ratio was only 0.2% (just in one female with 44 years of age) in the SCDs group (p<0.01) (Table 2). The mean age of RA was 44.5 ± 7.6 (30-57) years in the control group. On the other hand, transfused RBCs 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). 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 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†	433
Female ratio	48.5% (208)	Ns	48.4% (210)
Mean age of males	30.6 ± 10.1 (5-58)	Ns	30.4 ± 11.1 (9-59)
Mean age of females	30.1 ± 9.9 (8-59)	Ns	30.3 ± 10.4 (9-58)
Prevalence of RA‡	*0.2% (1)*	*<0.01*	*2.7% (12)*

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Rheumatoid arthritis

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)

*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 premature aging and related morbidity and mortalities in human beings. Physical inactivity, excess weight, smoking, alcohol consumption, chronic inflammatory and infectious processes, and cancers may accelerate the process. Probably, it is the most common type of vasculitis all over the world. 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 continuous endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature which reduces blood flow and increases systolic BP further. Although early withdrawal of the causative factors may retard the final consequences, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed completely due to their fibrotic nature (12).

SCDs are life-threatening hereditary disorders affecting around 100,000 individuals in the United States (13). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (14), because the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced severe and continuous endothelial damage, inflammation, edema, and fibrosis terminate with end-organ failure in early years of ages. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature (15), 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 RBCs support during medical and surgical emergencies in Hatay region. Actually, RBCs support must be given during all medical and surgical events in which there is evidence of clinical deterioration in the SCDs (16, 17). RBCs 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 RBCs transfusions are superior to exchange. First of all, preparation of one or two units of RBCs suspensions 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 RBCs suspensions each time decreases the severity of pain and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusion of lesser units of RBCs suspensions each time decreases transfusion-related complications. Fourthly, transfusion of RBCs 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 (15) and longer overall survival of females in the world (18) cannot be explained by the atherosclerotic effects of smoking and alcohol alone, instead it may be explained by higher physical efforts of male sex in life that may terminate with an exaggerated sickling and vascular endothelial damage in early years of life (19).

RA is a common and chronic syndrome, characterized by non-specific but usually symmetric inflammation and synovial hypertrophy of the peripheral joints, potentially terminating with progressive destruction of articular and periarticular tissues with or without systemic manifestations (20). It typically affects small joints of the hands and feet, but it can also affect larger joints (21). Fever, subcutaneous and visceral nodules, pleural and pericardial effusions, lymphadenopathy, splenomegaly, cytopenias, and episcleritis are just some of the samples of the extra-articular manifestations. Diagnosis is based on duration of symptoms, joint distribution, acute phase reactants, and autoantibodies including RF and anti-CCP (22). The presence of clinical or subclinical synovitis seen with ultrasonography or MRI is essential for diagnosis. RA can sometimes present with a large joint monoarthritis or oligoarthritis. In cases presenting with monoarthritis, careful assessment for differential diagnosis is needed, particularly in the elderly patients where other conditions such as gout, calcium pyrophosphate deposition disease, and osteoarthritis are common (23). Early referral of patients with suspected synovitis, particularly in small joints of hands and feet, is important in long-term outcomes (24). On the other hand, RA may mimic several systemic disorders, particularly in young and middle-aged females due to the extra-articular manifestations. According to our experiences, the diagnosis of RA requires highly trained specialists who are able to differentiate early symptoms of RA from other pathologies, particularly from SLE. SLE can be distinguished by the characteristic skin lesions on light-exposed areas, oral aphthous lesions, nonerosive arthritis, positive antibodies to double-stranded DNA, renal and central nervous system involvement, and thrombocytopenia. Especially clinicians in the hematology clinics should be aware of SLE due to the frequent thrombocytopenia in differential diagnosis with idiopathic thrombocytopenic purpura. Although RA and SLE have similar agents in the treatment protocol, antinuclear antibody and anti-double-stranded DNA antibody should be studied in every patient suspected with RA. According to our observations, methotrexate may be the simplest, cheapest, and one of the most effective treatment regimens for both disorders. It can suppress inflammation and may allow reduction of corticosteroid doses. It can be used orally. In the course of severe active diseases, methotrexate should be used early since its benefit often begins in 3 to 4 weeks. It can be given 2.5 to 20 mg in a single dose once weekly, starting at 7.5 mg/wk and gradually increased as needed.

SCDs are severe inflammatory processes terminating with significant health problems in early years of life in both genders (25). For example, menarche is significantly retarded in females with the SCDs (26). Additionally, the severe and continuous endothelial 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 rapidly progress into the severe and life-threatening infections including pneumonia, meningitis, and sepsis due to the relative immunodeficiency in such patients (27). Tonsillary hypertrophy is a frequent physical examination finding that may be the result of a prolonged infectious process due to the relative immunodeficiency of such patients (28). 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, RBCs supports, medications, prevented normal daily activities, and an eventually suppressed mood of the body can even suppress the immune system of the body (29, 30). In another definition, SCDs may cause moderate to severe immunosuppression with several mechanisms in the human body.

As a conclusion, SCDs are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failures in early years of life. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms that may be the cause of significantly lower prevalence of RA in the SCDs.

References

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-1428.
2. Helvaci MR, Kaya H, Sevinc A, Camci C. Body weight and white coat hypertension. Pak J Med Sci 2009; 25(6): 916-921.
3. Helvaci MR, Gokce C, Davran R, Akkucuk S, Ugur M, Oruc C. Mortal quintet of sickle cell diseases. Int J Clin Exp Med 2015; 8(7): 11442-11448.
4. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27(2): 361-364.
5. Zhao J, Su Y, Li R, Ye H, Zou Q, Fang Y, et al. Classification criteria of early rheumatoid arthritis and validation of its performance in a multi-centre cohort. Clin Exp Rheumatol 2014; 32(5): 667-73.
6. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 4D(9): 1725.
7. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4): 347-65.
8. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179(7): 615-621.
9. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 2008; 19(5): 325-329.
10. Schamroth L. Personal experience. S Afr Med J 1976; 50(9): 297-300.
11. Mankad VN, Williams JP, Harpen MD, Manci E, Longenecker G, Moore RB, et al. Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations. Blood 1990; 75(1): 274-283.
12. Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. HealthMED 2012; 6(12): 3977-3981.
13. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312(10): 1033-1048.
14. Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 2013; 7(8): 2327-2332.
15. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330(23): 1639-1644.
16. Charache S, Scott JC, Charache P. ‘‘Acute chest syndrome’’ in adults with sickle cell anemia. Microbiology, treatment, and prevention. Arch Intern Med 1979; 139(1): 67-69.
17. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1(8367): 36-38.
18. Mathers CD, Sadana R, Salomon JA, Murray CJ, Lopez AD. Healthy life expectancy in 191 countries, 1999. Lancet 2001; 357(9269): 1685-1691.
19. Helvaci MR, Ayyildiz O, Gundogdu M. Gender differences in severity of sickle cell diseases in non-smokers. Pak J Med Sci 2013; 29(4): 1050-1054.
20. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62(9): 2569-81.
21. Kourilovitch M, Galarza-Maldonado C, Ortiz-Prado E. Diagnosis and classification of rheumatoid arthritis. J Autoimmun 2014; 48-49: 26-30.
22. Sun J, Zhang Y, Liu L, Liu G. Diagnostic accuracy of combined tests of anti cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis: a meta-analysis. Clin Exp Rheumatol 2014; 32(1): 11-21.
23. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018; 4: 18001.
24. Evans J, Negoescu A. Early referral improves long-term outcomes in rheumatoid arthritis. Practitioner 2017; 261(1804): 21-5.
25. Helvaci MR, Yaprak M, Abyad A, Pocock L. Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Med 2018; 16(3): 12-18.
26. Helvaci MR, Davarci M, Inci M, Yaprak M, Abyad A, Pocock L. Chronic endothelial inflammation and priapism in sickle cell diseases. World Family Med 2018; 16(4): 6-11.

27. Helvaci MR, Acipayam C, Aydogan A, Akkucuk S, Oruc C, Gokce C. Acute chest syndrome in severity of sickle cell diseases. Int J Clin Exp Med 2014; 7(12): 5790-5795.
28. Helvaci MR, Gokce C, Davran R, Acipayam C, Akkucuk S, Ugur M. Tonsilectomy in sickle cell diseases. Int J Clin Exp Med 2015; 8(3): 4586-4590.
29. Helvaci MR, Acipayam C, Davran R. Autosplenectomy in severity of sickle cell diseases. Int J Clin Exp Med 2014; 7(5): 1404-1409.
30. Helvaci MR, Aydogan A, Akkucuk S, Oruc C, Ugur M. Sickle cell diseases and ileus. Int J Clin Exp Med 2014; 7(9): 2871-2876.