ATHEROSCLEROTIC BACKGROUND OF CIRRHOSIS IN SICKLE CELL PATIENTS

Mehmet Rami Helvaci (1)
Alper Sevinc (1)
Celaletdin Camci (1)
Ali Keskin (1)
Abdulrazak Abyad (2)
Lesley Pocock (3)

(1) Specialist of Internal Medicine, MD
(2) Middle-East Academy for Medicine of Aging, MD
(3) Medi-WORLD International

Corresponding author:
Prof Dr Mehmet Rami Helvaci,
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

Received: February 2021; Accepted: March 2021; Published: April, 2021
Citation: Helvaci MR et al. Atherosclerotic background of cirrhosis in sickle cell patients. Middle East Journal of Nursing 2021; 15(2): 21-25.DOI: 10.5742/MEJN2021.937807

Abstract

Background: We tried to understand the presence of any atherosclerotic background of cirrhosis in patients with sickle cell diseases (SCDs).

Methods: The study was performed in the Hematology Service of the Mustafa Kemal University on SCDs patients between March 2007 and June 2012.

Results: The study included 256 patients with SCDs (127 females). Their mean age was 29.3 years. Cirrhosis was detected in 5.8% (15) of the SCDs patients without any gender difference (6.2% of females versus 5.4% of males, $p>0.05$). There were 15 (5.8%) patients with chronic obstructive pulmonary disease with a highly significant male predominance (3.1% versus 8.5%, $p<0.001$). Digital clubbing and pulmonary hypertension were also higher in males, but the differences were nonsignificant in between (4.7% versus 6.2% and 11.0% versus 12.4%, respectively). Similarly, the leg ulcers were significantly higher in males, too (5.5% versus 16.2%, $p<0.001$). The significant male predominance was also observed in stroke and smoking (3.1% versus 6.2%, $p<0.05$ and 3.9% versus 11.6%, $p<0.001$, respectively). There were 14 (5.4%) mortal patients during the five-year follow-up period (6.2% of females and 4.6% of males, $p>0.05$), and the mean ages were 31.0 and 26.8 years, respectively ($p>0.05$).

Conclusion: Probably cirrhosis is a systemic inflammatory process prominently affecting the hepatic vasculature, and an eventual accelerated atherosclerotic process is the main underlying cause of characteristics of the disease. SCDs are accelerated systemic atherosclerotic processes, too, and the higher prevalence of cirrhosis in SCDs patients may indicate the underlying atherosclerotic background of cirrhosis.

Key words: Atherosclerosis, metabolic syndrome, cirrhosis, sickle cell diseases

Introduction

Atherosclerosis may be the major underlying cause of aging of human beings that decreases quality and duration of lifespan. Probably it is an irreversible process that is accelerated by many factors. Smoking, dyslipidemia, obesity, diabetes mellitus (DM), hypertension (HT), and various systemic inflammatory or infectious disorders may be the accelerating causes of the systemic process. Such preventable causes of the systemic atherosclerotic process are mainly collected under the heading of metabolic syndrome (1-6). The syndrome is characterized by a group of metabolic risk factors including overweight, dyslipidemia, elevated blood pressure, insulin resistance, and a prothrombotic and proinflammatory state for the development of irreversible diseases such as obesity, HT, DM, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), peripheric artery disease (PAD), and stroke (7). Similary, cirrhosis is also a frequent and continuously increasing cause of morbidity and mortality in the world (8), and it may not solely be a hepatic disease instead it may just be one of the terminal consequences of a systemic atherosclerotic process.

Sickle cell diseases (SCDs) are chronic endothelial dysfunctions that are characterized by sickle-shaped red blood cells which is caused by homozygous inheritance of the hemoglobin S (Hb S). Polymerisation of the Hb S distorts red blood cells into a sickle shape and decreases their elasticity. The polymerisation process probably takes place during the whole life, although its severity may increase during stressful conditions. The abnormal shape and decreased elasticity cause chronic endothelial damage terminating with an accelerated atherosclerotic process that may be the underlying cause of significantly shortened survival in SCDs patients (9). We tried to understand the presence of any atherosclerotic background of cirrhosis in patients with SCDs in the present study.

Material and methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and June 2012. All patients with SCDs were enrolled into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography. Their medical histories including smoking habit, regular alcohol consumption, leg ulcers, and stroke were learnt, and cases with a history of one pack-year were accepted as smokers. A check up procedure including liver function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an abdominal ultrasonography, a Doppler ultrasonography to evaluate the portal blood flow, an endoscopy to detect esophageal varices just in suspected cases, and a computed tomography of the brain was performed. Cases with acute painful crisis, infections, or inflammatory events were treated at first, and then spirometric pulmonary function tests to diagnose COPD and a Doppler echocardiography to measure the systolic blood pressure of pulmonary artery were performed on a silent phase. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (10). Systolic blood pressure of the pulmonary artery at and above 40mmHg during the silent phase was accepted as pulmonary hypertension (11). Clubbing is diagnosed by determining the ratio of distal phalangeal diameter to interphalangeal diameter which is required to be >1.0 and with the presence of Schamroth's sign (12,13). Cirrhosis is diagnosed with serum laboratory tests, ultrasonographic findings, esophageal varices, and ascites without any histologic procedure in the absence of any indication. Eventually, SCDs patients with pulmonary hypertension, leg ulcers, smoking, cirrhosis, COPD, clubbing, stroke, and exitus were detected and compared between the sexes. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 256 patients with SCDs (127 females and 129 males). The mean age of them was 29.3 ± 9.5 (14-59) years. There was not any patient with regular alcohol consumption. Cirrhosis was detected in 5.8% (15) of the SCDs patients without any gender difference (6.2% of females versus 5.4% of males, $p>0.05$) (Table 1). Although antiHCV was positive in two of the cirrhotic cases, HCV RNA was negative by polymerase chain reaction method in both of them. Histological diagnosis of cirrhosis was required in none of the study cases. On the other hand, there were 15 (5.8%) patients with COPD with a highly significant male predominance (3.1% versus 8.5%, $p<0.001$). Digital clubbing and pulmonary hypertension were also higher in males, but the differences were nonsignificant in between (4.7% versus 6.2% and 11.0% versus 12.4%, respectively). Similarly, the leg ulcers were significantly higher in males, too (5.5% versus 16.2%, $p<0.001$). The significant male predominance was also observed in stroke and smoking (3.1% versus 6.2%, $p<0.05$ and 3.9% versus 11.6%, $p<0.001$, respectively). On the other hand, there were 14 (5.4%) mortal patients during the five-year follow-up period without any significant gender difference (6.2% of females and 4.6% of males, $p>0.05$), and the mean ages were 31.0 and 26.8 years, respectively ($p>0.05$) (Table 2).

Table 1: Characteristic features of the sickle cell cases

Variables	Prevalence	Mean age (year)	Female cases	Male cases	*p*-value
Pulmonary hypertension	11.7% (30)	30.4 ±10.9 (19-56)	11.0% (14)	12.4% (16)	ns*
Leg ulcers	10.9% (28)	*35.7 ± 7.6 (17-58)*	*5.5% (7)*	*16.2% (21)*	*<0.001*
Smoking	7.8% (20)	*33.1 ± 9.3 (21-54)*	*3.9% (5)*	*11.6% (15)*	*<0.001*
Cirrhosis	5.8% (15)	33.6 ±12.5 (19-56)	6.2% (8)	5.4% (7)	ns
COPD†	5.8% (15)	*35.0 ± 8.7 (23-54)*	*3.1% (4)*	*8.5% (11)*	*<0.001*
Clubbing	5.4% (14)	36.1 ±12.1 (21-56)	4.7% (6)	6.2% (8)	ns
Stroke	4.6% (12)	*32.5 ± 9.2 (17-47)*	*3.1% (4)*	*6.2% (8)*	*<0.05*

*Nonsignificant (p>0.05) †Chronic obstructive pulmonary disease

Table 2: Features of the mortal patients

Variables	Female cases	Male cases	*p*-value
Prevalence	6.2% (8)	4.6% (6)	ns*
Mean age (year)	31.0 ±10.6 (19-45)	26.8 ±7.1 (19-39)	ns

*Nonsignificant (p>0.05)

Discussion

Probably cirrhosis is a systemic inflammatory process prominently affecting the hepatic vasculature, and an eventual accelerated atherosclerotic process is the main underlying cause of characteristics of the disease. The origin of the inflammation is unclear but aging, smoking, regular alcohol consumption, local or systemic inflammatory or infectious processes, and excess weight may be the major ones of the several possible causes. The inflammatory process is enhanced by release of various chemical factors by lymphocytes to repair the damaged hepatic tissues, especially endothelial cells of the hepatic arteriols (14). Due to the continuous irritation process of the endothelial cells in the case of aging, smoking, regular alcohol consumption, local or systemic inflammatory or infectious processes, or excess weight, prominent changes develop in the architecture of the hepatic tissue, since the chronic inflammatory process of the endothelial cells terminates with atherosclerosis, tissue hypoxia, and fibrosis. Metabolic abnormalities such as dyslipidemia, hyperglycemia, and insulin resistance cause various cellular stress responses that induce tissue inflammation and immune cell activation, which in turn exacerbate the atherosclerotic process (15). Although cirrhosis is mainly an accelerated atherosclerotic process of the hepatic vasculature, there are several items of evidence about existence of an associated systemic endothelial inflammation. For example, there may be a close relationship between cirrhosis and CHD, COPD, PAD, chronic renal disease, and stroke probably due to the underlying systemic atherosclerotic process (16). Additionally, most of the mortality cases in cirrhosis may actually be caused by cardiovascular diseases, and CHD may be the most common one among them (8). Similarly, beside the digital clubbing, pulmonary hypertension, leg ulcers, stroke, and COPD like atherosclerotic end-points, cirrhosis is just one of the final consequences of the SCDs, as accelerated systemic atherosclerotic processes, in the present study.

Both the frequency and complications of cirrhosis are increasing in the world. For example, cirrhosis and chronic liver disease were the 10th leading cause of death for men and the 12th for women in the United States in 2001, killing about 27,000 people each year (8). Although the achieved development of health services worldwide, the increased mortality and morbidity of cirrhosis may only be explained by aging of the human being and increased frequency of excess weight in the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to a third of the world population, and it has become the most common cause of chronic liver disease even in children and adolescents (17,18). The recent rise in the prevalence of excess weight likely explains the NAFLD epidemic worldwide (16). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammatory state, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (17). NAFLD shares many features of the metabolic syndrome as a highly atherogenic condition, and may cause hepatic inflammation and liver cell injury especially at the endothelial level. Beside terminating with cirrhosis, NAFLD is associated with a significantly greater overall mortality as well as with an increased prevalence of cardiovascular diseases (18). Authors have reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased carotid artery intimal medial thickness as the reliable markers of subclinical atherosclerosis (18), so NAFLD may also be a predictor of cardiovascular disease (19,20). NAFLD and cirrhosis may be considered as the hepatic components of the accelerated systemic atherosclerotic process, metabolic syndrome, and hepatic fat is highly correlated with all components of the syndrome (21). On the other hand, the systemic inflammatory effects of smoking on endothelial cells is already known with Buerger's disease and COPD (7). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic inflammatory and eventual atherosclerotic process in smokers. The inflammatory and eventually atherosclerotic effects of alcohol is prominent in hepatic endothelium probably due to the higher concentrations of its metabolites in liver. Similarly, aging may be another but unpreventable cause of systemic atherosclerotic process that prevents adequate tissue repair. The prevented adequate tissue repair may be a significant cause of the increased risk of cancers in elders, since immune cells cannot eradicate the malignant ones effectively due to the prevented adequate tissue circulation. Chronic inflammatory or infectious disorders may also terminate with an accelerated systemic atherosclerotic process (14). For example, chronic HCV infection had raised carotid intima-media thickness, indicating a direct effect of infection, and hepatic function normalisation with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (14).

Hb S causes red blood cells to change their elastic biconcave disc shape to a hard sickle shape especially during mild, moderate, and severe stresses. The red blood cells can take their normal elastic shapes later, but after repeated cycles of sickling and unsickling attacks, they get a permanent sickle shape with a loss of elastic motion ability that is especially important during the passage between the endothelial cells. So they cause damage on the vascular endothelial cells terminating with a chronic endothelial inflammation. Because of the lifelong duration of the chronic endothelial inflammation, an accelerated atherosclerotic process develops all over the body in SCDs patients. Although the chronic inflammatory process is exaggerated during infections, operations, or depressions like various stresses, it is usually present during the whole lives of the patients. The chronic process is usually shown by a permanent leukocytosis and thrombocytosis even in silent phases of the patients (22). The adverse effects of neutrophils on endothelium are of particular interest with regard to CHD and stroke in SCDs. For example, leukocytosis during the silent phase was an independent predictor of the severity of the disease in a previous study (23), and it was associated with the risk of stroke in another study

(24). On the other hand, due to the accelerated systemic atherosclerotic processes, SCDs may be a useful model to show the end results of systemic atherosclerosis seen with the metabolic syndrome even in early age groups (9). The very high prevalences of cirrhosis (5.8%), COPD (5.8%), digital clubbing (5.4%), pulmonary hypertension (11.7%), leg ulcers (10.9%), stroke (4.6%), and exitus (5.4%) even in the early age group (29.3 years) may be a good sample to show some end-points of the systemic atherosclerosis in the present study.

As a conclusion, probably cirrhosis is a systemic inflammatory process prominently affecting the hepatic vasculature, and an eventual accelerated atheroscerotic process is the main underlying cause of characteristics of the disease. SCDs are accelerated systemic atherosclerotic processes, too, and the higher prevalence of cirrhosis in SCDs patients may indicate the underlying atherosclerotic background of cirrhosis.

References

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365: 1415-1428.

2. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004; 109: 433-438.

3. Helvaci MR, Kaya H, Gundogdu M. Association of increased triglyceride levels in metabolic syndrome with coronary artery disease. Pak J Med Sci 2010; 26: 667-672.

4. Helvaci MR, Kaya H, Borazan A, Ozer C, Seyhanli M, Yalcin A. Metformin and parameters of physical health. Intern Med 2008; 47: 697-703.

5. Helvaci MR, Seyhanli M. What a high prevalence of white coat hypertension in society! Intern Med 2006; 45: 671-674.

6. Helvaci MR, Kaya H, Sevinc A, Camci C. Body weight and white coat hypertension. Pak J Med Sci 2009; 25: 916-921.

7. Helvaci MR, Aydin LY, Aydin Y. Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome. Pak J Med Sci 2012; 28: 376-379.

8. Anderson RN, Smith BL. Deaths: leading causes for 2001. Natl Vital Stat Rep 2003; 52: 1-85.

9. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27: 361-364.

10. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2010. Global initiative for chronic obstructive lung disease (GOLD).

11. 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: 615-621.

12. Schamroth L. Personal experience. S Afr Med J 1976; 50: 297-300.

13. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 2008; 19: 325-329.

14. Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, Godsland I, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut 2010; 59: 1135-1140.

15. Xia M, Guerra N, Sukhova GK, Yang K, Miller CK, Shi GP, et al. Immune activation resulting from NKG2D/ligand interaction promotes atherosclerosis. Circulation 2011; 124: 2933-2943.

16. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9: 372-381.

17. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J 2012; 33: 1190-1200.

18. Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011; 17: 3082-3091.

19. Maurantonio M, Ballestri S, Odoardi MR, Lonardo A, Loria P. Treatment of atherogenic liver based on the pathogenesis of nonalcoholic fatty liver disease: a novel approach to reduce cardiovascular risk? Arch Med Res 2011; 42: 337-353.

20. Mawatari S, Uto H, Tsubouchi H. Chronic liver disease and arteriosclerosis. Nihon Rinsho 2011; 69: 153-157.

21. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des 2010; 16: 1941-1951.

22. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. Pren Med Argent 2014; 100: 49-56. Spanish

23. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ, et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342: 83-89.

24. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, Serjeant GR. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992; 120: 360-366.