Atherosclerosis in sickle cell disease – a review

Mohamed A Elsharawy MS MD FRCS FICA¹, Khaled M Moghazy MS MD², Mohamed A Shawarby MD PhD³

MA Elsharawy, KM Moghazy, MA Shawarby. Atherosclerosis in sickle cell disease – a review. Int J Angiol 2009;18(2):62-66.

Acute, vaso-occlusive crises are the most common and earliest clinical manifestations of sickle cell disease. Recent thoughts about development of atherosclerosis as a result of this disease are presented. Current insights into the pathogenesis of atherosclerosis in sickle cell disease

are reviewed, in particular the role of endothelial dysfunction, homocysteine and platelets. Common and uncommon sites of atherosclerosis are described. Radiological assessment and potential therapeutic agents to slow the progression of atherosclerosis are discussed. Finally, treatment of atherosclerosis in certain sites is evaluated and reviewed.

Key Words: Atherosclerosis; Peripheral arterial disease; Sickle cell disease

Ischemic complications are the major causes of morbidity and mortality in patients with sickle cell disease (SCD) (1). The pathogenesis of these complications is poorly understood. Ischemic events in these patients have been attributed to the effects of hemoglobin polymerization, resulting in rigid, dense and sickled cells trapped in the microcirculation. Therefore, vascular occlusion is often considered to be synonymous with occlusion of microvasculature by sickled red blood cells (2). Several observations suggest that other factors may also play a pathogenic role. Atherosclerosis is one of these factors and may affect many arteries all over the body (3). We review the most relevant pathogenesis and common sites, as well as management of atherosclerosis in patients with SCD.

PATHOGENESIS

Endothelial dysfunction in SCD

The sickling process leads to vascular occlusion, tissue hypoxia and subsequent reperfusion injury, thus inducing inflammation and endothelial injury (4). This causes a blunted response to nitric oxide (NO) synthase inhibition (5). In recent years, investigators' attention has been attracted by the effects of chronic hemolysis on vascular bed integrity and function in patients with congenital hemolytic anemias. Hemolysis results in the release of free hemoglobin. On one hand, it scavenges NO by oxidizing it to nitrate and releasing red blood cell arginase. On the other hand, it hydrolyzes L-arginine, the substrate of NO synthase. Because of these effects, NO bioavailability and its action is limited (6). All the previous mechanisms cause impairment of NO production (7,8). NO is an important vascular relaxing factor and its deficiency would lead to large artery stiffness (5,9,10). In addition, NO promotes general vascular homeostasis by decreasing endothelial expression of adhesion molecules, decreasing platelet activation (5), and inhibiting fibroblast, smooth muscle cell and endothelial cell mitogenesis and proliferation (11-13).

In addition, sickled erythrocytes increase endothelin-1 and platelet-derived growth factor-B production (14,15). Both are potent vasoconstrictors, strong mitogens for fibroblast and smooth muscle cells, and serve as fibroblast

chemoattractants (15-17). At the same time, chronic hypoxia increases secretion of vascular endothelial-derived growth factor and thrombospondin-1. Both have mitogenic effects on smooth muscle and connective tissue, unopposed by the antiproliferative effects of NO, which may result in smooth muscle hypertrophy and structural remodelling (18).

All of the above are likely to contribute to the progressive development of sickle cell vasculopathy, characterized by vasoconstriction, intimal and smooth muscle hyperplasia and in situ thrombosis.

Another mechanism of endothelial dysfunction is that the sickled red blood cells are most likely to adhere to endothelium at sites of high flow turbulence. Repeated adhesion followed by forcible removal under high shear forces may cause endothelial injury leading to intimal hyperplasia and endothelial narrowing (2,19). This is usually found in vessels with high flow rates, such as cerebral vessels. In these cases, occlusion of the vasa vasorum is not believed to account for intimal hyperplasia. The vasa vasorum are not found in middle and anterior cerebral arteries and they appear patent in the stenosed and occluded internal carotid artery (20).

A further mechanism of endothelial dysfunction is attributed to the rigidity of sickled erythrocytes causing mechanical injury to the endothelial cells. This chronic physical injury to the endothelial cells may modify the immune identity of the endothelium or subendothelium, thus eliciting an immune attack that could in turn perpetuate a vicious circle by causing more damage (21). However, most of the investigators agreed that more studies are required (2,19).

Role of homocysteine

Elevation in the plasma concentration of homocysteine is an established risk factor for venous thrombosis and arteriosclerosis (22,23). However, the mechanisms involved in this risk still remain a mystery. Several studies have shown that the increased risk of atherosclerosis is due to direct toxicity of homocysteine in tissues, low S-adenosylmethionine or high S-adenosylhomocysteine, or thrombotic events triggered by stimulation of procoagulant factors and suppression of anticoagulant factors and platelet activation, thereby enhancing

Departments of ¹Surgery; ²Radiology; and ³Pathology, King Faisal University, Al-Khobar, Kingdom of Saudi Arabia

Correspondence: Dr Mohamed A Elsharawy, PO Box 40081, Al-Khobar 31952, Eastern Province, Kingdom of Saudi Arabia.

Telephone 00-96-650-185-2057, fax 00-96-63-896-6728, e-mail elsharawya@yahoo.co.uk

oxidative stress, smooth muscle cell proliferation and formation of reactive oxygen species (24).

Patients with SCD have elevated plasma concentrations of homocysteine (25,26) and, if they have a history of stroke, plasma concentrations of homocysteine are significantly higher than in those without a history of stroke (26). The cause of hyperhomocysteinemia in SCD is not clear. Some authors believe that it may be due to folic acid deficiency (27) or blood transfusion (28). Others proved that there was no difference in plasma homocysteine concentrations between transfused and nontransfused subjects with SCD, and there was no correlation between plasma folate and homocysteine concentrations (23).

Role of platelets

Platelets play a pivotal role in atherothrombosis. The activation of platelets releases an array of agonists, such as ADP; adhesive molecules, such as P-selectin, thrombospondin, fibrinogen and von Willebrand factor; coagulation factors; and growth factors. In turn, they present transmembrane receptors for a plethora of agonists and ligands (29).

Markers of platelet activation, such as P-selectin expression on circulating platelets, increased plasma concentrations of platelet factor 4 and beta-thromboglobulin, and increased numbers of circulating platelet microparticles, have been detected in patients with SCD (30). Activation of platelets increases CD40L in plasma (31), which induces an inflammatory phenotype on endothelial cells (32) and enhances the adhesion of sickled red cells to the inflamed endothelium (33).

SITES OF ATHEROSCLEROTIC DISEASE

The pulmonary artery is one of the common sites of atherosclerosis in SCD. Autopsy of the pulmonary artery in patients with SCD showed that approximately one-third of the patients had histological evidence of medial hypertrophy, intimal proliferation, and subintimal proliferation and fibrosis (34). Another site of involvement in patients with SCD is the splenic artery, which shows intimal proliferation and disruption of internal elastic lamina with or without medial hypertrophy or fibrosis (21). Cerebral arteries are considered to be the most common sites of large vessel disease and the lesions are very similar to those observed in the splenic artery (35,36). Approximately 75% of strokes in SCD are the result of occlusion of large vessels (37).

Peripheral arterial disease in SCD patients is uncommon. Only one case has been reported (3); another patient was managed by the authors. Iliofemoral endarterectomy was performed for critical ischemia in the left foot. Microscopic examination of the endarterectomy specimen revealed vascularized fibro-osseous tissue with focal calcification, residual fibrin deposits, scattered foreign body giant cells and mild focal mononuclear inflammatory cellular infiltration. There were also separate fragments of vascularized fibromuscular tissue with mild mononuclear inflammatory cellular infiltration (Figure 1).

MANAGEMENT

Radiological assessment of vascular lesions is challenging due to heavy calcification of the vessels. Doppler ultrasonography is widely available and noninvasive. However, there are limitations for its use in SCD. Imaging of the aortoiliac segment is frequently compromised owing to overlying bowel gas, and

Figure 1) A Vascularized fibrous (★) and osseous (arrowhead) tissue, giant cells (curved arrow), mild mononuclear inflammatory cell infiltration (arrow) and fibrin. Stained with hematoxylin and eosin; original magnification $\times 100$. **B** Focal calcification. Stained with hematoxylin and eosin; original magnification $\times 200$. **C** Fibromuscular tissues. Stained with hematoxylin and eosin; original magnification $\times 100$. **D** Fibromuscular tissue stained with antismooth muscle actin monoclonal antibody. Note the positively stained smooth muscle fibres. Immunohistochemistry with 3,3'-diaminobenzidine as chromagen; original magnification $\times 200$

extensive vessel calcification may prevent detection of stenosis (38). Both magnetic resonance (MR) (20) and computed tomographic (CT) (39) angiography are increasingly used as minimally invasive techniques for vascular imaging, providing a precise road map for vascular intervention (Figures 2 to 4). However, MR angiography is costly and vessel calcification may not be visualized (40). Low confidence in CT angiography can occur in cases of extensive vessel wall calcifications. A calcified vessel wall indicates severe disease, but this feature can be an impediment to stenosis measurement (39,41,42). Digital subtraction angiography is still the gold standard for vascular assessment of the peripheral arteries and has the advantage of providing accurate information on the vascular lesions (43) (Figure 5). Nevertheless, it is invasive and technically demanding due to vessel wall calcification.

Unfortunately, there is no standard treatment for atherosclerosis in SCD. Management of the vascular lesion is difficult. Medications or changes in lifestyle, such as exercise, cannot control or improve the condition. Intensification of SCD therapy by long-term exchange transfusion can reduce the synthesis of sickle cells and their pathological effects (44). The risk of most complications of the disease can also be reduced, including the risks of pulmonary events and central nervous system vasculopathy (45-47). Even if exchange transfusion therapy does not lower hemolytic rates sufficiently to inhibit the development of vasculopathy, a higher hemoglobin level and higher oxygen-carrying capacity are likely to reduce morbidity and possibly mortality by prevention of comorbid events (48). In patients with SCD and hyperhomocysteinemia, oral supplementation with folic acid has been shown to lower the plasma homocysteine concentration even in the absence of folic acid deficiency (49).

Figure 2) Cranial involvement of a patient with sickle cell disease. **A** Axial T2-weighted magnetic resonance imaging showing a high signal intensity wedge-shaped area of old infarction at the left parietal (arrowheads) and the right frontal (arrow) lobes. **B** Magnetic resonance angiography showing block of the left internal carotid and right anterior cerebral arteries. **C** Axial noncontrast computed tomography of the neck with coronal reformatted (**D**) showing bilateral extensive calcification along both common carotid arteries (arrows)

Figure 3) Axial noncontrast computed tomography of the chest of a patient with sickle cell disease showing calcification of the main pulmonary trunk (arrow)

Patients with symptomatic pulmonary hypertension are usually treated with therapies that include intravenous prostacyclins (iloprost, epoprostenol, treprostinil) (50), phosphodiesterase-5 inhibitors (sildenafil) (51,52) and endothelin-1 antagonist (bosentan) (53). However, no controlled efficacy data exist for any of these drugs.

In patients with peripheral arterial disease, revascularization is not easy because of the diffuse calcified nature of the vascular disease and age of presentation. The authors prefer endarterectomy rather than bypass in children and adolescents, especially

Figure 4) Noncontrast axial computed tomography of the abdomen of a patient with sickle cell disease. **A** Calcification along the splenic artery (arrows) and gall bladder stone (arrowhead). **B** Calcification along both renal arteries (arrows). **C** Coronal reformatted computed tomography showing calcification along the superior mesenteric artery (arrow)

Figure 5) Peripheral arterial involvement of a patient with sickle cell disease. **A,B** Digital subtraction angiography showing total block of both common femoral and right superficial femoral arteries with multiple collaterals. **C** Noncontrast coronal reformatted computed tomography of the abdomen showing calcification along the right common iliac (arrowheads) and both common femoral (arrows) arteries. **D** Computed tomography angiography after iliofemoral endarterectomy showing patent left iliac and femoral arteries (arrow)

in the iliofemoral region, which has a good long-term patency rate (54).

CONCLUSION

SCD is an uncommon risk factor for atherosclerosis. The pathogenesis is poorly understood. Endothelial dysfunction,

hyperhomocysteinemia and activation of platelets are the most likely mechanisms for the development of atherosclerosis. Cerebral arteries, pulmonary arteries and the splenic artery are the most common sites of atherosclerosis in SCD. Peripheral arterial disease is uncommon. Radiological assessment of vascular lesions is challenging due to heavy calcification of the vessels. Both MR and CT angiography are increasingly used as minimally invasive techniques for vascular imaging. However, digital subtraction angiography is still the gold standard for vascular assessment of the peripheral arteries. Unfortunately, there is no standard treatment for atherosclerosis in SCD. Long-term exchange transfusion can reduce the synthesis of sickle cells and their pathological effects. Oral supplementation with folic acid has been shown to lower the plasma homocysteine concentration. In patients with peripheral arterial disease, revascularization will not be easy because of the diffuse calcified nature of the vascular disease and age of presentation.

REFERENCES

- Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1639-44.
- Francis RB Jr, Johnson CS. Vascular occlusion in sickle cell disease: Current concepts and unanswered questions. *Blood* 1991;77:1405-14.
- Elsharawy MA, Moghazy KM. Peripheral arterial lesions in patient with sickle cell disease. *Eur J Vasc Endovasc Surg Extra* 2007;14:15-8.
- Stuart MJ, Setty BN. Sickle cell acute chest syndrome: Pathogenesis and rationale for treatment. *Blood* 1999;94:1555-60.
- Gladwin MT, Kato GJ. Cardiopulmonary complications of sickle cell disease: Role of nitric oxide and hemolytic anemia. *Hematology Am Soc Hematol Educ Program* 2005:51-7.
- Morris CR, Kato GJ, Poljakovic M, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. *JAMA* 2005;294:8-90.
- Lipowsky HH, Sheikh NU, Katz DM. Intravital microscopy of capillary hemodynamics in sickle cell disease. *J Clin Invest* 1987;80:117-27.
- Rodgers GP, Schechter AN, Noguchi CT, Klein HG, Nienhuis AW, Bonner RF. Periodic microcirculatory flow in patients with sickle-cell disease. *N Engl J Med* 1984;311:1534-8.
- Fitch RM, Vergona R, Sullivan ME, Wang YX. Nitric oxide synthase inhibition increases aortic stiffness measured by pulse wave velocity in rats. *Cardiovasc Res* 2001;51:351-8.
- Aessopos A, Farmakis D, Tsironi M, et al. Endothelial function and arterial stiffness in sickle-thalassemia patients. *Atherosclerosis* 2007;191:427-32.
- Garg UC, Hassid A. Nitric oxide-generating vasodilators inhibit mitogenesis and proliferation of BALB/C 3T3 fibroblasts by a cyclic GMP-independent mechanism. *Biochem Biophys Res Commun* 1990;171:474-9.
- Sarkar R, Webb RC, Stanley JC. Nitric oxide inhibition of endothelial cell mitogenesis and proliferation. *Surgery* 1995;118:274-9.
- Lau YT, Ma WC. Nitric oxide inhibits migration of cultured endothelial cells. *Biochem Biophys Res Commun* 1996;221:670-4.
- Faller D. Endothelial cell responses to hypoxic stress. *Clin Exp Pharmacol Physiol* 1999;26:74-84.
- Ergul S, Brunson CY, Hutchinson J, et al. Vasoactive factors in sickle cell disease: In vitro evidence for endothelin-1-mediated vasoconstriction. *Am J Hematol* 2004;76:245-51.
- Peacock AJ, Dawes KE, Shock A, Gray AJ, Reeves JT, Laurent GJ. Endothelin-1 and endothelin-3 induce chemotaxis and replication of pulmonary artery fibroblasts. *Am J Respir Cell Mol Biol* 1992;7:492-9.
- Dzau VJ, Gibbons GH. Endothelium and growth factors in vascular remodeling of hypertension. *Hypertension* 1991;18:115-21.
- Kariya K, Kawahara Y, Araki S, Fukuzaki H, Takai Y. Antiproliferative action of cyclic GMP-elevating vasodilators in cultured rabbit aortic smooth muscle. *Atherosclerosis* 1989;80:143-7.
- Francis RB. Large-vessel occlusion in sickle cell disease: Pathogenesis, clinical consequences, and therapeutic implications. *Med Hypotheses* 1991;35:88-95.
- Moritani T, Hiwatashi A, Shrier DA, Wang HZ, Numaguchi Y, Westesson PL. CNS vasculitis and vasculopathy: Efficacy and usefulness of diffusion-weighted echoplanar MR imaging. *Clin Imaging* 2004;28:261-70.
- de Chadarevian JP, Balarezo FS, Heggere M, Dampier C. Splenic arteries and veins in pediatric sickle cell disease. *Pediatr Dev Pathol* 2001;4:538-44.
- den Heijer M, Koster T, Blom HJ, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. *N Engl J Med* 1996;334:759-62.
- Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: An independent risk factor for vascular disease. *N Engl J Med* 1991;324:1149-55.
- Huang T, Yuan G, Zhang Z, Zou Z, Li D. Cardiovascular pathogenesis in hyperhomocysteinemia. *Asia Pac J Clin Nutr* 2008;17:8-16.
- Lowenthal EA, Mayo MS, Cornwell PE, Thornley-Brown D. Homocysteine elevation in sickle cell disease. *J Am Coll Nutr* 2000;19:608-12.
- Houston PE, Rana S, Sekhsaria S, Perlin E, Kim KS, Castro O. Homocysteine in sickle cell disease: relationship to stroke. *Am J Med* 1997;103:192-6.
- Lindenbaum J, Klipstein FA. Folic acid deficiency in sickle-cell anemia. *N Engl J Med* 1963;269:875-82.
- Malinow MR, Axthelm MK, Meredith MJ, MacDonald NA, Upson BM. Synthesis and transsulfuration of homocysteine in blood. *J Lab Clin Med* 1994;123:421-9.
- Jennings LK. Role of platelets in atherothrombosis. *Am J Cardiol* 2009;2(3 Suppl):4A-10A.
- Wun T, Paglieroni T, Rangaswami A, et al. Platelet activation in patients with sickle cell disease. *Br J Haematol* 1998;100:741-9.
- Lee SP, Ataga KI, Orringer EP, Phillips DR, Parise LV. Biologically active CD40 ligand is elevated in sickle cell anemia: Potential role for platelet-mediated inflammation. *Arterioscler Thromb Vasc Biol* 2006;26:1626-31.
- André P, Nannizzi-Alaimo L, Prasad SK, Phillips DR. Platelet-derived CD40L: The switch-hitting player of cardiovascular disease. *Circulation* 2002;20:896-9.
- Bennett JS. Vasoocclusion in sickle cell anemia: Are platelets really involved? *Arterioscler Thromb Vasc Biol* 2006;26:1626-31.
- Graham JK, Mosunjac M, Hanzlick RL, Mosunjac M. Sickle cell lung disease and sudden death: A retrospective/prospective study of 21 autopsy cases and literature review. *Am J Forensic Med Pathol* 2007;28:168-72.
- Stockman JA, Nigro MA, Mishkin MM, Oski FA. Occlusion of large cerebral vessels in sickle cell anemia. *N Engl J Med* 1972;287:846-9.
- Rothman SM, Fulling KH, Nelson JS. Sickle cell anemia and central nervous system infarction: A neuropathological study. *Ann Neurol* 1986;20:684-90.
- Moran CJ, Siegel MJ, DeBaun MR. Sickle cell disease: Imaging of cerebrovascular complications. *Radiology* 1998;206:311-21.
- Sesier Y, Hartshorne T, Thrush A, Nydahi S, Bolia A, London NJM. A prospective comparison of lower limb colour-coded duplex scanning with arteriography. *Eur J Vasc Endovasc Surg* 1996;11:170-5.
- Elsharawy MA, Moghazy KM. Can multi-detector computed tomographic angiography replace conventional angiography prior to lower extremity arterial reconstruction? *Acta Chir Belg* 2006;106:193-8.
- de Vries M, Ouwendijk R, Flobbe K, et al. Peripheral arterial disease: Clinical and cost comparisons between duplex US and contrast-enhanced MR angiography – a multicenter randomized trial. *Radiology* 2006;240:401-10.
- Ouwendijk R, Kock MC, van Dijk LC, van Sambeek MR, Stijnen T, Hunink MG. Vessel wall calcifications at multi-detector row CT angiography in patients with peripheral arterial disease: Effect on clinical utility and clinical predictors. *Radiology* 2006;241:603-8.
- Heijnenbroek-Kal MH, Kock MC, Hunink MG. Lower extremity arterial disease: Multidetector CT angiography meta-analysis. *Radiology* 2007;245:433-9.

43. Adriaensen ME, Kock MC, Stijnen T, et al. Peripheral arterial disease: Therapeutic confidence of CT versus digital subtraction angiography and effects on additional imaging recommendations. *Radiology* 2004;233:385-91.
 44. Benza RL. Pulmonary hypertension associated with sickle cell disease: Pathophysiology and rationale for treatment. *Lung* 2008;186:247-54.
 45. Pegelow CH, Adams RJ, McKie V, et al. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. *J Pediatr* 1995;126:896-9.
 46. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5-11.
 47. Aessopos A, Farmakis D, Hatziliani A, et al. Cardiac status in well-treated patients with thalassemia major. *Eur J Haematol* 2004;73:359-66.
 48. Machado RF, Gladwin MT. Chronic sickle cell lung disease: New insights into the diagnosis, pathogenesis and treatment of pulmonary hypertension. *Br J Haematol* 2005;129:449-64.
 49. Brattstrom LE, Israelsson B, Jeppsson JO, Hultberg BL. Folic acid – an innocuous means to reduce plasma homocysteine. *Scand J Clin Lab Invest* 1988;48:215-21.
 50. Badesch DB, McLaughlin VV, Delcroix M, et al. Prostanoid therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;43:56S-61S.
 51. Machado RF, Martyr S, Kato GJ, et al. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. *Br J Haematol* 2005;130:445-53.
 52. Barnett CF, Machado RF. Sildenafil in the treatment of pulmonary hypertension. *Vasc Health Risk Manag* 2006;2:411-22.
 53. Channick R, Williamson TL. Diagnosis and treatment of pulmonary arterial hypertension *Cardiol Clin* 2004;22:441-52.
 54. Stoney RJ, Reilly LM. Endarterectomy for aortoiliac disease. In: Ernst CG, Stanley JC, eds. *Current Therapy in Vascular Surgery*. Philadelphia: BC Decker, 1987:157.
-