Premature peripheral arterial disease – difficult diagnosis in very early presentation

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Peripheral arterial disease (PAD) is defined as an ankle-brachial index of less than 0.9. It is mostly prevalent in patients older than 50 years of age; its occurrence in younger patients is rare. Nevertheless, the diagnosis must be considered in any patient with exertional lower extremity symptoms. Patients with early-onset disease, also called premature PAD, have a particularly difficult course with early involvement of other major arterial beds such as the carotid and coronary arteries. Their diagnosis and treatment have to be comprehensive to prevent

early morbidity and mortality. Reports of very early occurrence and management are rare, especially of onset before 25 years of age. Management of this early presentation of PAD is unclear because most of the available information concerns treatment of patients 40 years of age or older. The cases of two patients who developed symptomatic PAD before 25 years of age are described, and the various causes and management options available for the treatment of early onset PAD patients are discussed.

Key Words: Claudication; Early; Peripheral arterial disease; Premature; Young

Premature peripheral arterial disease (PAD) is the onset of peripheral arterial occlusion before the age of 50 years. Its prevalence is rare (less than 1% of the population), with most of those affected falling between 30 to 49 years of age (1). The onset of PAD before 25 years of age is extremely rare and there have been no epidemiological studies characterizing its prevalence. Management of this early presentation of PAD is unclear because most of the available information concerns treatment of patients 40 years of age or older. We present two patients with the onset of PAD symptoms before the age of 25 years, along with a discussion of clinical management considerations.

CASE PRESENTATIONS

Case 1

A 26-year-old woman presented with complaints of bilateral calf pain after walking one to two blocks that was relieved with approximately 5 min of rest. She noted the onset of these symptoms at 16 years of age after running short distances. Since then, her claudication advanced insidiously, progressively limiting her exercise capacity and walking distance. She denied any history of chest pain, shortness of breath, lower extremity edema, trauma, radiation exposure, ergot use for migraine or regular bicycling. In addition, she also had no known personal or family history of hypertension, diabetes, hyperlipidemia, deep vein thrombosis, hypercoagulable state, Raynaud's phenomenon, collagen vascular disease or other autoimmune disorders. Her family history was also negative for cardiovascular disease, including PAD. She smoked one to two cigarettes per day for a year during her mid teens, then stopped. She did not use any illicit drugs and was not taking medications at the time of the examination.

Her physical examination revealed a pulse of 74 beats/min and a bilateral brachial blood pressure of 122/80 mmHg. A

detailed vascular examination revealed no carotid or abdominal bruits. Radial, brachial and femoral artery pulses were normal bilaterally. However, popliteal and dorsalis pedis pulses were not palpable on the right side and were decreased on the left side. The remainder of her physical examination was unremarkable. Her laboratory values were within the normal range including hemoglobin 140 g/L, platelet count $323 \times 10^9/L$, creatinine 79.56 $\mu\text{mol/L}$, glycosylated hemoglobin A₁ 4.8%, low-density lipoprotein (LDL) 2.72 mmol/L, high-density lipoprotein 1.26 mmol/L, triglycerides 0.94 mmol/L, prothrombin time 11.4 s, partial thromboplastin time 26.30 s, international normalized ratio 0.93 and homocysteine 6.9 $\mu\text{mol/L}$. Antinuclear antibodies, high-sensitivity C-reactive protein, erythrocyte sedimentation rate, fibrinogen level, beta-2 microglobulin and lipoprotein (a) were within normal limits. A hypercoagulable panel assessing for protein C or S deficiency, antithrombin III deficiency, prothrombin gene mutation, factor V Leiden mutation, anticardiolipin antibody and the lupus anticoagulant was negative. Right ankle-brachial index (ABI) was 0.65 and left ABI was 0.72. Magnetic resonance angiography of her lower extremities showed severe bilateral superficial femoral artery (SFA) disease with prominent collaterals and three-vessel run-off bilaterally (Figure 1).

Case 2

A 33-year-old man reported having claudication that was more severe in the right calf than the left calf with jogging since the age of 22 years. His symptoms progressed over 11 years and he currently is limited to 100 m to 200 m of jogging without rest. Similar to case 1, he had no other symptoms of cardiovascular disease. His personal and family history was negative for cardiovascular risk factors including smoking. He had previously been diagnosed with borderline hyperlipidemia, with LDL at 4.17 mmol/L, and was taking statin medication. His

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Figure 1 Magnetic resonance angiogram of case 1 showing bilateral superficial femoral artery occlusive disease with good inflow and three-vessel run-off bilaterally

physical examination revealed a pulse of 70 beats/min and a bilateral brachial blood pressure of 136/86 mmHg. A detailed vascular examination revealed no carotid or abdominal bruits. Radial, brachial and femoral artery pulses were normal bilaterally. However, the popliteal and dorsalis pedis arterial pulses were nonpalpable bilaterally. There was no pedal cyanosis, clubbing or edema. The remainder of the physical examination was unremarkable. The right ABI was 0.82 and the left ABI was 0.80. Magnetic resonance angiography revealed severe left aortoiliac and SFA disease, as well as a right distal SFA and popliteal artery occlusion. A detailed laboratory evaluation identical to that of case 1 was performed, with all values within normal limits.

DISCUSSION

PAD is defined as an ABI of less than 0.90 in either leg. It affects the quality of life by decreasing functional capabilities and has the potential to cause loss of limbs (2). The 2007 Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) on PAD estimated that 27 million individuals are affected in Europe and North America (3). Management of PAD focuses on modification of risk factors to prevent cardiovascular morbidity and mortality as well as treatments that improve functional status. Patients with premature PAD have a particularly difficult course, with early involvement of

other arterial beds such as the carotid and coronary arteries (4). Thus, their diagnosis and treatment have to be comprehensive to prevent early morbidity and mortality. Recognition of claudication symptoms in young patients is the initial key to the diagnosis of premature PAD. While leg pain in young patients is often attributed to 'muscle cramps/spasms', trauma or arthritis, PAD must always be high on the differential diagnosis list when evaluating a patient of any age with effort-induced lower extremity symptoms. In younger patients, similar to older patients, PAD is most likely to arise from atherosclerotic disease, but other considerations for ischemic lower extremity disease include Buerger's disease in smokers, collagen vascular diseases and thrombophilic disorders (5,6). Patients with premature PAD must be assessed for general cardiovascular risk factors, as well as risk factors unique to premature PAD. These include hypertension, smoking, diabetes, chronic renal failure, trauma, hypercoagulable states, vasculitis, hyperlipidemia and ergot use for migraine (1,7-9). High levels of homocysteine, high-sensitivity C-reactive protein, fibrinogen and lipoprotein (a) are associated with premature PAD (10). A rare cause of PAD is kinking of the iliac artery in cyclists leading to endofibrosis. Its occurrence is underestimated and should be considered in cyclists with leg pain (11). Early onset of viral and bacterial infections such as cytomegalovirus, *Chlamydia pneumoniae* and *Helicobacter pylori* may predispose to PAD (12).

In the two above cases, the patients developed PAD at an unusually early age and did not have any obvious modifiable risk factors. Management of such patients includes the initiation of an exercise program; intermittent walking to near-maximal pain for at least six months can improve their pain-free walking distance (13,14). Various pharmacological therapies have been shown to slow disease progression, prevent cardiovascular events and increase functional capacity. Antiplatelet therapy with acetylsalicylic acid or clopidogrel should be started in all patients with PAD who do not have contraindications (15). Statin therapy to decrease LDL levels to below 2.6 mmol/L is also recommended. Statins may have the additional benefit of improving leg function in PAD patients (16). Cilostazol, a phosphodiesterase 3 inhibitor, may improve claudication symptoms in patients with PAD (17). Ultimately, if patients remain highly limited in their functional capacity, endovascular or open surgical revascularization of the lower extremities can be considered. A variety of research strategies are now being implemented to stimulate new collateral channels in ischemic lower limbs. The genetic influences on PAD development and progression are largely unknown. New findings in this area may alter the present course of the disease and influence its future management.

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