Severe atherosclerotic changes, including aortic occlusion, associated with hyperhomocysteinaemia and antiphospholipid antibodies

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Abstract
Three patients are described with severe systemic atherosclerosis, including aortic occlusion, in the presence of a spectrum of risk factors, including hypercholesterolaemia, hypertension, a positive family history of cardiovascular problems, and hyperhomocysteinaemia. In all three patients high levels of anticardiolipin antibodies were found. The possible pathogenic role of antiphospholipid antibodies in atherosclerosis in the context of hyperhomocysteinaemia in these patients is discussed.

We describe three patients with severe systemic atherosclerosis including one with aortic occlusion. High levels of antiphospholipid antibodies (aPLs) and hyperhomocysteinaemia were present in all three patients, who were also heavy smokers. To our knowledge, this is the first report in which the relation between severe atherosclerosis, aPLs, and hyperhomocysteinaemia is discussed. There has been much debate about the possible pathophysiological role of aPLs in atherosclerosis. The presence of these autoantibodies and other known atherogenic factors in our patients is discussed.

Case reports

PATIENT 1
A 41 year old man was seen at our outclinic because of hypertension. He smoked 10 cigarettes a day with a history of 25 pack years. His father also had had hypertension and angina pectoris. Apart from the hypertension (blood pressure 220/110 mm Hg), a physical examination was unremarkable. In particular, no bruits were heard over the renal arteries. The patient was taking amlodipine 5 mg/day and atenolol 100 mg/day. Ultrasound examination of his abdomen showed a smaller left kidney (12.7 cm right side; 9.2 cm left side), which had shrunk since a similar investigation one year previously (12.3 cm). As renal artery stenosis was suspected, angiography was performed.

Injection of contrast into the descending thoracic aorta showed that the aorta was occluded. Huge intercostal arteries feeding collaterals over the abdominal wall to the pelvic and leg arteries were found. Severe atheromatous plaques, an occluded left renal artery, a partially (70%) occluded right renal artery, an occluded coeliac trunk, and partially (50%) occluded superior mesenteric artery were found (fig 1).

In view of these findings, additional laboratory tests were carried out (table 1). Homocysteine levels were very high, and folate levels were slightly decreased. After folate treatment (5 mg once a day), homocysteine levels normalised (although still in the higher range) as measured by the methionine loading test. Anticardiolipin antibodies of both IgM and IgG class were present at high levels (repeated testing), whereas lupus anticoagulant and Venereal Disease Research Laboratory results were negative. High density lipoprotein (HDL) cholesterol concentration was decreased and triglycerides were increased. Treatment with coumarins was started.

The risk of complications during or after extensive vascular surgery were explained to the patient. He declined the offer of surgical intervention. So far (one year later), he is doing well.

PATIENT 2
This 50 year old man with intermittent claudication presented at the outclinic for evaluation. His walking distance had decreased to 200 m. He had a smoking history of 50 pack years. Various family members had had vascular problems before the age of 60: his mother had undergone coronary artery bypass grafting three times; his sister had peripheral vascular disease requiring several angioplasties; his daughter has hyperhomocysteinaemia without...
PATIENT 1
This 62 year old woman presented at our outpatient clinic for evaluation of progressive intermittent claudication. These symptoms had been present for eight years. Her smoking history was 20 pack years. There was a family history of myocardial infarction. She had a 10 year history of hypertension and angina pectoris with recent posterior myocardial infarction. Coronary arteriography showed an occluded right coronary artery, with collateral filling, and an 80% occluded circumflex artery, which was stented after percutaneous transluminal coronary angioplasty. Apart from weak peripheral pulsations and bruits over the abdomen and femoral arteries, a physical examination was unremarkable. Aortic angiography showed a bilateral renal artery stenosis (right side 50%, left side 70%) and considerable aortic atherosclerotic changes with subtotal occlusion of the right common iliac artery. The latter abnormality was treated with balloon dilatation and stent placement. Table 1 gives the laboratory data. As in the other patients, hyperhomocysteinaemia was present, and anticardiolipin IgGs were repeatedly found. Testing for lupus anticoagulant was negative. Homocysteine levels normalised after treatment with pyridoxine and folate.

PATIENT 2
This 74 year old man presented with a right leg ulcer. He has a history of hypercholesterolemia, which was treated with clofibrate. Apart from an aortic valve pseudostenosis 20 years ago, with a normal echocardiogram, there was no clinical evidence of vascular disease. This patient has no family history of vascular disease. He has a family history of myocardial infarction at age 70. His smoking history was 20 pack years. Recent examination was unremarkable. Aortic angiography showed an occluded right renal artery and 50% stenosis of both common iliac arteries. The latter was not treated. Table 1 shows the laboratory data. Again, progressive atherosclerosis was seen, with normal homocysteine levels and negative testing for lupus anticoagulant. Homocysteine levels normalised after treatment with pyridoxine and folate.

PATIENT 3
This 62 year old woman presented at our outpatient clinic for evaluation of progressive intermittent claudication. These symptoms had been present for eight years. Her smoking history was 20 pack years. There was a family history of myocardial infarction. She had a 10 year history of hypertension and angina pectoris with recent posterior myocardial infarction. Coronary arteriography showed an occluded right coronary artery, with collateral filling, and an 80% occluded circumflex artery, which was stented after percutaneous transluminal coronary angioplasty. Apart from weak peripheral pulsations and bruits over the abdomen and femoral arteries, a physical examination was unremarkable. Aortic angiography showed a bilateral renal artery stenosis (right side 50%, left side 70%) and considerable aortic atherosclerotic changes with subtotal occlusion of the right common iliac artery. The latter abnormality was treated with balloon dilatation and stent placement. Table 1 gives the laboratory data. As in the other patients, hyperhomocysteinaemia was present, and anticardiolipin IgGs were repeatedly found. Testing for lupus anticoagulant was negative. Homocysteine levels decreased considerably after treatment with pyridoxine/folate, but remained above the normal range. So far, her intermittent claudication has improved considerably.

Discussion
Renovascular hypertension is most often due to atherosclerosis and fibromuscular dysplasia. Less common causes include renal artery thrombosis. One of the causes of arterial thrombosis is the presence of aPLs, including anticardiolipin antibodies. aPLs occur most often in systemic autoimmune diseases, such as systemic lupus erythematosus, and in “primary” antiphospholipid syndrome.

Occlusion of the aorta in the presence of aPLs is rare. aPLs and deposition of endothelial immune complex have both been suggested to play a role in atherosclerosis in patients with lupus. However, the process of this atherogenicity remains obscure. Premature atherosclerosis of the lower limbs as the first symptom of the antiphospholipid syndrome has been reported. This indicates the possible involvement of aPLs in the pathogenesis of progressive atherosclerosis in these patients. The concurrent presence of antibodies to low density lipoprotein (anti-LDL) and deposition of LDL/anti-LDL immune complexes with subsequent endothelial damage may also play a role.

Another possible pathogenic cofactor is dyslipidaemia—that is, the presence of aPLs with increased levels of triglycerides, as found in one of our patients—has been shown to increase the risk of premature thrombosis.

The probable antigenic target of anticardiolipin antibodies is β2 glycoprotein 1 (β2GP1), a 50 kDa plasma protein that has anticoagulant effects in vitro. Anti-β2GP1 antibodies may increase the uptake of oxidised LDLs by macrophages, thereby forming foam cells and contributing to atherosclerosis. In addition, George et al showed a proatherogenic effect of immunisation with βGP1 in a mouse model.

In our patients, none of the other features of “primary” antiphospholipid syndrome or systemic lupus erythematosus were found, whereas several risk factors for atherosclerosis were present. It has been suggested that aPLs may not only be a cause of, but also a sequel to, severe atherosclerosis. The production of aPLs may be triggered by endothelial damage and exposure of antigens to the immune system. Atherosclerotic plaque instability and rupture concurs with local apoptosis of endothelial cells and inflammatory cells such as macrophages and T lymphocytes. During the late apoptotic process, characteristic changes, called blebbing, occur in the phospholipid phase of the cell membrane. These surface blebs on apoptotic cells show high procoagulant activity and have been associated with the production of aPLs.

In addition to the aforementioned factors contributing to atherosclerosis, low HDL cholesterol levels, heavy smoking, and hyperhomocysteinaemia were present in our patients. The latter syndrome has recently been recognised as an important inherited autosomal recessive disorder increasing the risk of atherosclerotic events (reviewed by Boers). Hyperhomocysteinaemia is characteristic of homocystinuria, because of homozgyosity for cystathionine synthase deficiency or other rarer enzymatic abnormalities in the methionine-homocysteine pathway.
metabolic pathway. Mild hyperhomocysteinaemia, either during fasting or after a standardised oral methionine load (typically 100 mg/kg), can be the result of intermediate deficiency of one of the enzymes mentioned above. Severe hyperhomocysteinaemia leads to a 50% chance of vascular problems before the age of 30. Hence, even mild hyperhomocysteinaemia is considered an important risk factor in atherogenesis. Increased homocysteine levels can be reduced by vitamins, including B12, B6, and folate. In two of our patients, folate levels were slightly decreased (table 1), probably because of an inadequate diet. After vitamin treatment, homocysteine levels decreased considerably. The duration of hyperhomocysteinaemia is not known in our patients. Recent data underline the importance of high homocysteine levels as a risk factor for mortality in patients with coronary artery disease. Notably, this association was found irrespective of possible coexisting folate deficiency. Accumulating data suggest that homocysteine may affect endothelial resistance to thrombosis. Hyperhomocysteinaemia may thus be an important cofactor in the pathogenesis of the vascular abnormalities in our patients.

The possible association between hyperhomocysteinaemia and the presence of aPLs has been studied previously. Although homocysteine levels were higher in lupus patients with renal failure, no association with the presence of aPLs was found. In another study, aPLs were not found in patients with renal failure and mild hyperhomocysteinaemia. These cases illustrate that severe (premature) atherosclerosis often results from a spectrum of causes. Established risk factors include hypertension, smoking, and a family history of cardiovascular problems. Hyperhomocysteinaemia and the presence of aPLs should also be considered, because these can be treated with drugs. If aPLs are persistently present (repeated testing), coumarins should be started. A reduction in cardiovascular problems after treatment of hyperhomocysteinaemia remains to be proven (studies are underway). Meanwhile, it seems wise to prescribe folate and pyridoxine for all patients with manifest atherosclerosis. Hyperhomocysteinaemia may thus be an important cofactor in the pathogenesis of the vascular abnormalities in our patients.

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