Hyperhomocysteinaemia and multiple aneurysms

Niall Colwell, Robert Clarke, Killian Robinson, Frank Keane, Sean O'Briain and Ian Graham

Cardiology Department, The Adelaide Hospital, Peter Street, Dublin 8, Ireland

Summary: Homozygous homocystinuria, the most common genetic disorder of transulphuration, is associated with elevated plasma concentrations of homocystine, homocysteine, multiple clinical abnormalities and life-threatening thromboembolism. Several instances of vascular aneurysms have also been documented. More recently, an association between premature occlusive vascular disease and the heterozygous state has been proposed. We now report an unusual case in whom multiple aneurysms were associated with heterozygous homocystinuria.

Introduction

Homocystinuria is an autosomal recessive condition most commonly caused by cystathionine B synthase deficiency.¹ It is frequently complicated by early onset vascular disease and life-threatening thromboembolism,² and in a number of reports, aneurysms have been reported.³ Although a link has been suggested between the heterozygous state and premature vascular disease⁴ a possible connection between this and the presence of aneurysms has not yet been proposed.

Case report

A 64 year old male was referred with a 1 year history of right groin swelling, and intermittent claudication. There was no relevant past or family history and he had ceased smoking 30 years previously.

Physical examination revealed a blood pressure of 170/100 mmHg and the presence of readily palpable abdominal aortic, right iliac, right femoral as well as right and left popliteal aneurysms. There were no clinical features of any other connective tissue disorders.

Laboratory tests including blood glucose and cholesterol concentrations, erythrocyte sedimentation rate and autoantibody screen were normal and the VDRL and TPHA tests for treponemal infection were negative. Chest X-ray was normal while the electrocardiogram showed changes consistent with an old inferior myocardial infarction.

Peripheral vascular angiography demonstrated diffuse dilatation of the lower aorta and the common and external iliac vessels. The arteries of both lower limbs showed such marked reduction in the circulation time that the distal calf and pedal circulations could not be demonstrated. Aneurysmal dilatation of the left common iliac, right common femoral, the left and right superficial femorals (Figure 1) and both popliteals were noted. Ultrasonography confirmed the arteriographic findings and also detected a 1 cm right brachial aneurysm.

Homocysteine, measured as the mixed disulphide, was undetectable in the blood prior to methionine loading. The peak value was 39.0 $\mu\text{mol/l}$ which is in

Figure 1 Contrast angiogram demonstrating aneurysmal dilatation affecting the lower abdominal aorta, both common iliac arteries and the internal and external iliac arteries.

Figure 2 An elastic stain shows a poorly defined internal elastic lamina (arrow) and damaged elastic fibres within the media. (Elastic van Gieson $\times 28$.)

the range reported for obligate heterozygotes for homocystinuria.⁵ The activity of cystathionine B synthase, as measured in endothelial cell cultures obtained at operation, was markedly reduced at 1.52 nmol/h/mg (reference values in normals 3–20), a level consistent with heterozygosity for homocystinuria (B. Fowler, personal communication). This value increased only slightly to 1.92 nmol/h/mg after the addition of 1 mmol of pyridoxal phosphate, a cofactor of cystathionine B synthase. Elective repair of the aortic, iliac and right femoral aneurysms by end-to-end anastomosis of a bifurcated dacron graft was undertaken. Femoropopliteal by-pass of the right and left popliteal aneurysms using autogenous reverse saphenous vein grafts from the superficial femoral vessels above to the popliteal vessels below was performed. Post-operative recovery was unremarkable.

A section of the excised aneurysm wall was fixed in formalin and stained by haematoxylin and eosin, periodic acid Schiff, alcian blue and elastic van Gieson (Figure 2). There was moderate intimal thickening with patchy lipid deposits and fibro-elastosis. The media was well preserved with moderate numbers of muscle cells. There was some fragmentation adjacent to elastic fibres associated with small foci of myxoid degeneration and occasional aggregates of chronic inflammatory cells. Elastic stains revealed a poorly developed internal elastic lamina and within the media elastic fibres were extensively damaged showing branching, attenuation, fragmentation and smudging. A

damaged internal elastic lamina was also present in the arterioles of the adventitia, which was otherwise normal.

One year later right femoropopliteal graft occlusion occurred and was managed conservatively with success.

Discussion

Homocystinuria, a rare autosomal recessive condition, is the most frequent genetic disorder of transsulphuration.¹ Most often due to deficiency of cystathionine B synthase, it is associated with multiple clinical abnormalities including ectopia lentis, osteoporosis, mental retardation and premature occlusive vascular disease as well as aneurysm formation and potentially life-threatening thromboembolism. The heterozygous state has recently been associated also with the development of premature vascular disease.⁴

The activity of cystathionine synthase in this case was markedly reduced and in the range seen in obligate heterozygotes, i.e. parents of homocystinuric patients. Furthermore, this persisted even after treatment with pyridoxine. In addition, the extent and severity of distribution of the aneurysms were unusual and while this patient was also hypertensive, the latter was unlikely to be the sole factor in the aetiology of the aneurysms.⁶ The intimal and medial changes resemble those previously described in hyperhomocysteinaemia.^{7,8} Similar changes may also occur in arteriosclerosis although the degree of medial damage and in particular the elastic degeneration appear disproportionately severe for the moderate degree of intimal thickening. This elastic damage may have played a permissive role in the development of aneurysms in this patient. Accumulation of myxoid material and zonal loss of elastic tissue as seen in cystic medial degeneration were not observed in this case. The occurrence of the heterozygous state for homocystinuria may thus be a previously unrecognized cause for peripheral vascular aneurysms, although possible synergy of hypertension with this could have been a contributing factor. Surgery is associated with an increased incidence of thromboembolic events in homocystinuric patients⁹ and, although operation was performed safely in this case, the observation of subsequent graft occlusion raises the possibility that the heterozygote state may be a risk factor for this as well.

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