



Editorial

Homocysteine, Marfan Syndrome and arteriosclerosis

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Homocystinuria is an inherited disease of homocysteine metabolism most commonly caused by deficiency of the pyridoxal phosphate-dependent enzyme, cystathionine synthase. The disease is manifested in many cases by accelerated growth in childhood, dislocated ocular lenses, skeletal abnormalities, retarded mental development, and propensity to thrombosis with increased mortality from vascular disease.¹ Before the discovery of homocystinuria in 1962, many of these subjects were considered to have Marfan Syndrome, because of accelerated growth, dislocated ocular lenses, and vascular disease. Subsequent screening of the urine for homocysteine revealed a number of cases of homocystinuria that were originally attributed to Marfan Syndrome.²

Review of an archival case of homocystinuria originally reported in 1933 disclosed generalized arteriosclerosis and death from carotid thrombosis and stroke in an eight-year-old boy with mental retardation, dislocated ocular lenses, and skeletal abnormalities.³ Review of a second case of homocystinuria, caused by deficiency of methionine synthase, a folate- and cobalamin-dependent enzyme, disclosed severe and widespread arteriosclerotic plaques in arteries throughout the major organs. Because of the difference in metabolic pattern between these two cases of homocystinuria caused by different enzyme abnormalities, the amino acid homocysteine was concluded to have atherogenic properties because of a direct effect on the cells and tissues of the arteries.³ A subsequent case of a nine-year-old girl with homocystinuria caused by deficiency of methylenetetrahydrofolate reductase, a folate-dependent enzyme, was also found by other investigators to have widespread arteriosclerotic plaques, independently corroborating this conclusion.

Early reports of the pathological manifestations of homocystinuria attributed the vascular changes to a

lathryogenic effect of homocysteine on the connective tissues of arteries because of a molecular resemblance of homocysteine to penicillamine, a well-known lathryogenic compound.⁴ Subsequent study of the role of homocysteine, however, has shown that moderate elevations of blood homocysteine levels are a potent independent risk factor for human arteriosclerotic vascular disease in the general population.⁵

In classic cases of Marfan Syndrome the vascular manifestations are principally dilation of aorta and aortic valve with cystic medial necrosis and predisposition to dissecting aneurysm of aortic arch. In homocystinuria the vascular manifestations are principally accelerated arteriosclerosis with predisposition to arterial and venous thrombosis and, occasionally in older subjects, arteriosclerotic aneurysm of abdominal aorta.

In the study by Giusti et al. in the current issue of *European Heart Journal*, the observation of elevated blood homocysteine levels in Marfan Syndrome establishes a new relation of this disease with the pathogenesis of arteriosclerosis. The findings show that Marfan Syndrome patients with the most severe vascular changes, including aortic dissection, have significantly higher homocysteine levels than patients with mild changes or normal controls. In addition, Marfan Syndrome patients with the common homozygous polymorphism of methylenetetrahydrofolate reductase, C677T, have significantly higher homocysteine levels and increased severity of vascular disease. These findings suggest that the pathogenesis of the vascular changes in Marfan Syndrome involves the action of homocysteine at a molecular, cellular and tissue level.

Investigation of cultured skin fibroblasts from patients with cystathionine synthase deficiency and homocystinuria revealed an aggregated, granular form of extracellular proteoglycan associated with increased binding of sulphate groups.⁶ This change from fibrillar to aggregated molecular conformation has been attributed to a transition from helical to random coil configuration produced by sulphate binding to homocysteine thio-lactone that is bound by ionic bonding to protein carboxyl groups. In addition, the cultured cells were found to

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convert the sulphur atom of homocysteine thiolactone to phosphoadenosine phosphosulphate by a new pathway independent of cystathionine and cysteine formation, since the cells lack cystathionine synthase. The activity of this pathway has been suggested to involve thio-retinamide, the amide formed from retinoic acid and homocysteine thiolactone.⁶ Thus organic sulphate esters of glycosaminoglycans are derived in part from the sulphur atom of homocysteine.

The findings of Giusti et al. suggest the possibility that homocysteine is involved in production of aortic cystic medial necrosis and deposition of sulphated glycosaminoglycans that is prominent in Marfan Syndrome. The deficiency of fibrillin-1 in this disease affects the integrity of elastic lamellae of aorta, and activation of matrix metalloprotein activity may be involved in elastolysis, predisposing to aortic dissection. Elevation of plasma homocysteine in Marfan Syndrome may indicate increased utilization of homocysteine for synthesis of the sulphated glycosaminoglycan extracellular matrix of aorta. This abnormal matrix deposition may affect the integrity of elastic lamellae of aorta. Early arteriosclerotic plaques are also characterized by increased synthesis of sulphated glycosaminoglycan matrix of altered solubility in arteriosclerosis, in homocystinuria, and in experimental animals given homocysteine.⁶ In addition, the characteristic splitting and degeneration of elastic lamellae in arteriosclerotic plaques is found in association with deposition of the abnormal extracellular matrix. These common features in the pathological changes of aorta in Marfan Syndrome and arteriosclerosis may be related to a common pathway of homocysteine metabolism and utilization, suggesting a new area for investigation.

Homocysteine is a chemically reactive amino acid that is capable of reacting with free sulphhydryl groups of proteins to form mixed homocysteine cysteine linkages. In fact, most of the homocysteine carried in plasma is bound to the cysteinyl groups of albumin and other plasma proteins, and only a small fraction (about 10%) of homocysteine in plasma is in the free sulphhydryl form. The free mixed homocysteine cysteine disulfide and the disulfide of homocysteine, homocystine, are not detectable in normal plasma, but are present in plasma and urine of patients with homocystinuria. Whether free homocysteine could interact with cysteinyl groups of abnormal fibrillin-1 molecules in Marfan Syndrome needs to be addressed by further investigation, as suggested by Giusti et al.

The anhydride of homocysteine is homocysteine thiolactone, a highly reactive intramolecular lactone containing a five membered ring. Homocysteine thiolactone in the free base form is soluble in aqueous and hydrophobic phases of cells and tissues. Homocysteine thiolactone readily reacts with free amino groups of proteins

to form homocysteinylated lysine groups of proteins. In general, homocysteinylated amino groups of proteins decreases their biological activity and function. In addition, homocysteine thiolactone may dimerize, forming homocysteine diketopiperazine, which polymerizes by oxidation to form the insoluble homocysteine diketopiperazine polymer (reviewed in reference⁶). Whether this reaction is occurring in the aorta and other tissues in Marfan Syndrome is presently unknown, but the findings of Giusti et al. suggest that homocysteinylated fibrillin-1 may occur in this disease.

In atherosclerosis LDL particles that are small and dense are associated with more rapid and severe atherogenesis, compared with LDL particles that are larger and less dense. LDL contains homocysteine bound by peptide bonds to the lysyl groups of apoB protein to form homocysteinylated LDL (reviewed in reference⁶). Reaction of homocysteine thiolactone with normal human LDL produces LDL particles containing increased concentrations of homocysteine that are small, dense, and form aggregates that are phagocytosed by cultured monocytes. This process is believed to explain the uptake and deposition of homocysteinylated LDL within vascular macrophages during atherogenesis.⁶ Further investigation is needed to ascertain whether a similar process is of importance in the vascular pathology of Marfan Syndrome, as suggested by the findings of Giusti et al.

The final suggestion from the findings of Giusti et al. is that therapy to lower homocysteine levels may benefit the prognosis in Marfan Syndrome by preventing vascular degeneration and dissecting aneurysm. Convincing evidence has been presented that vitamin therapy with folate, cobalamin and pyridoxine delays restenosis following angioplasty in patients with coronary heart disease. Multiple interventional trials are currently in progress worldwide to determine whether this approach will prevent mortality and morbidity in atherosclerosis. Positive results from these trials may suggest a similar approach to preventing morbidity and mortality in Marfan Syndrome, opening a further field of investigation.

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