Coronary artery disease in twins

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SUMMARY In two pairs of monozygotic twins with coronary artery disease who were studied by coronary angiography, there were striking similarities in the clinical course, response to exercise, and distribution of coronary artery disease. Though it is difficult to distinguish between heredity as an independent risk factor and the other major risk factors, the similarities in each twin pair may be best explained by identical heredity.

Environmental and hereditary components are important in the natural history of coronary artery disease. Because of the complex pathophysiology and the long latent period before arterial lesions produce clinical disease, separating the relative importance of each is difficult. Studies of twins afford the opportunity of isolating these components. Though twin registry material provides valuable information about population characteristics, it often lacks documentation of anatomy and clinical course. Detailed case reports are important in this regard. This report describes the clinical course and coronary anatomy in two monozygotic male twin pairs with coronary artery disease.

Case reports

TWIN PAIR 1

Case 1

This twin first experienced angina in 1974 at the age of 32 years. An initial evaluation done at another institution in April 1975 disclosed raised levels of cholesterol and triglycerides, a normal resting electrocardiogram, and a positive treadmill exercise test. Risk factors included a 10-year history of smoking 20 cigarettes a day, but not hypertension or diabetes mellitus. The patient's father had diabetes mellitus and peripheral vascular disease and had died of a myocardial infarct at the age of 58 years. The patient's older brother had symptomatic coronary artery disease.

The patient was first seen at the Mayo Clinic in August 1975, at which time he was 169 cm tall and weighed 74 kg. His blood pressure was 118/84

mmHg. Examination of the cardiovascular system was normal with the exception of diminished dorsalis pedis pulses bilaterally. There were no stigmata of hyperlipidaemia.

Laboratory investigation showed normal uric acid and blood sugar levels, chest x-ray, resting electrocardiogram, and vectorcardiogram. The cholesterol level was 7.91 mmol/l (306 mg/100 ml) and the triglyceride level was 2.17 mmol/l (175 mg/100 ml) with a lipoprotein electrophoresis pattern consistent with type IV hyperlipidaemia (Table 1). A treadmill exercise test was positive, with the development of angina at a heart rate of 130/min and a flat ST segment depression in the inferior and lateral leads. After stopping exercise, the electrocardiogram promptly returned to normal.

At cardiac catheterisation in August 1975, the left ventricular haemodynamics and angiogram were normal. Selective coronary injections (Fig. 1) showed a dominant right system, with severe proximal right coronary artery disease and occlusion in the middle one-third (Table 2). The distal right coronary artery and posterior descending arteries were visualised by collateral vessels from both the proximal right coronary artery and the left coronary artery. Both proximal left anterior descending and circumflex arteries were diseased, but the stenosis was ≤ 50 per cent. The distal vessels were normal. The patient continued on a medical programme consisting of glyceryl trinitrate, exercise, and weight reduction.

Case 2

The twin brother of case 1 presented with subendocardial inferior myocardial infarction in March

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Table 1 Clinical summary of two twin pairs with coronary artery disease

	Twin pair 1		Twin pair 2	
	Case 1	Case 2	Case 3	Case 4
Age at onset (y)	32	33	48	47
Height (cm)	168.9	168.9	174.5	174.2
Weight (kg)	74.0	86.3	71.7	75.8
History of hypertension	Neg	Pos	Pos	Pos
20 cigarettes/day (no. of years)	10	10 to 15	None	15
Cholesterol (mmol/l)	7.91	6.10	6.11	6.83
Triglycerides (mmol/l)	2.17	2.32	2.61	2.95
Lipoprotein electrophoresis	Type IV	Type IV	Type IV	Type IV
Erythrocyte and leucocyte antigens	Identical	Identical	Identical	Identical
Chromosome polymorphisms (C and Q banding)	Identical	Identical	Identical	Identical
Treadmill exercise test	Pos, 3 mph, 10% grade, heart rate 130/min	Pos, 2½ mph, 10% grade, heart rate 120/min	Pos, 2½ mph, 10% grade, heart rate 140/min	Pos, 2 mph, 10% grade, heart rate 140/min

1975, at the age of 33 years, without a previous history of angina. After an uncomplicated hospital course, he had stable exertional angina until September 1975, when it began to deteriorate. Risk factors were similar to those described in case 1, with a 10- to 15-year history of smoking 20 cigarettes a day and type IV hyperlipoproteinemia, for which the patient had been treated with nicotinic acid for nine years. There was no history of diabetes mellitus, but unlike that in case 1, the patient had a history of labile hypertension.

The patient was first seen at the Mayo Clinic in October 1975, at which time he was 169 cm tall and weighed 86 kg. His blood pressure was 154/92 mmHg. Examination of the cardiovascular system was normal, with the exception of diminished dorsalis pedis pulses bilaterally. There were no stigmata of hyperlipidaemia.

Laboratory investigation disclosed a uric acid level of 0.57 mmol/l (9.6 mg/100 ml) and a fasting blood sugar level of 5.77 mmol/l (104 mg/100 ml). The cholesterol level was 5.90 mmol/l (228 mg/100

ml) and the triglyceride level was 2.54 mmol/l (205 mg/100 ml) (Table 1), with a lipoprotein electrophoresis pattern consistent with type IV hyperlipoproteinemia. Findings on a chest x-ray, a resting electrocardiogram, and a vectorcardiogram were normal. A treadmill exercise test was positive, with the development of angina at a heart rate of 120 a minute and a flat ST segment depression in the inferior and lateral leads. After stopping exercise, the electrocardiogram promptly returned to normal.

At catheterisation in October 1975, the left ventricular end-diastolic pressure was minimally raised to 17 mmHg, but the left ventricular angiogram showed no abnormality. Selective coronary injections (Fig. 1) showed a dominant right system with severe proximal right coronary artery disease and occlusion in the middle one-third (Table 2). The distal right coronary and posterior descending arteries were filled by collateral vessels from both the proximal right coronary artery and the left coronary arteries. High-grade lesions were seen in both the proximal left anterior descending and

Fig. 1 Schematic representation of coronary anatomy in the first twin pair. Left, case 1. Right, case 2.

Table 2 Coronary anatomy and left ventricular function in two twin pairs with coronary artery disease

	Twin pair 1		Twin pair 2	
	Case 1	Case 2	Case 3	Case 4
Dominance	Right	Right	Left	Balanced
RCA (% occlusion)	100	100	100	100
LAD (% occlusion)	50	75	60	90
LCfx (% occlusion)	50	80	70	60
Obtuse marginal (% occlusion)	Normal	90	90	Normal
LMCA (% occlusion)	Normal	Normal	Normal	40
LVEDP (mmHg)	Normal	17	19	Normal
Segmental wall motion	Normal	Normal	Apical hypokinesis	Apical and posteroseptal hypokinesis

RCA, right coronary artery; LAD, left anterior descending artery; LCfx, left circumflex artery; LMCA, left main coronary artery; LVEDP left ventricular end-diastolic pressure.

circumflex arteries and the first obtuse marginal artery. The distal vessels were normal. The patient subsequently underwent surgery, receiving saphenous vein bypass grafts to the marginal, left anterior descending, and right coronary arteries. Two months after operation, he was asymptomatic at follow-up examination. A treadmill exercise test was repeated, and the patient maintained a heart rate of 162 beats a minute for three minutes without symptoms and only non-specific T wave abnormalities.

The twin pair was tested for red cell antigens of the ABO, Rh, Kell, Kidd, Duffy, and MN blood groups. HLA typing for all antigens recognised by WHO was also done. All typings were identical, and the statistical likelihood of monozygosity was 97 per cent.¹ The probability of monozygosity was increased by showing identical polymorphisms on the Q- and C-banded karyotypes.

TWIN PAIR 2

Case 3

This twin first experienced angina in 1975 at the age of 48 years. Risk factors included hypertension for

30 years, but there was no history of smoking or diabetes mellitus. The patient's identical twin brother (case 4) had developed angina the previous year. There was no other family history of ischaemic heart disease.

The patient was first seen at the Mayo Clinic in August 1976, at which time he was 174 cm tall and weighed 72 kg. His blood pressure was 145/95 mmHg. On examination of the cardiovascular system there was a fourth heart sound and a systolic ejection murmur. His peripheral pulses were normal. There were no stigmata of hyperlipidaemia.

Laboratory investigation showed a normal blood sugar level and chest x-ray. An electrocardiogram showed an increased QT interval and non-specific repolarisation abnormalities. The cholesterol level was 6.10 mmol/l (236 mg/100 ml), and the triglyceride level was 2.61 mmol/l (211 mg/100 ml), with a lipoprotein electrophoresis pattern consistent with type IV hyperlipidaemia. A treadmill exercise test was positive, with the onset of angina at two and a half minutes of exercise and a heart rate of 140 beats a minute and a 2 mm flat ST segment depression in the anterior precordial leads.

Fig. 2 Schematic representation of coronary anatomy in the second twin pair. Left, case 3. Right, case 4.

Cardiac catheterisation showed raised left ventricular end-diastolic pressure to 19 mmHg and mild apical hypokinesis (Table 2). There was a dominant left coronary system (Fig. 2). The right coronary artery was obstructed proximally, with poor visualisation of the distal vessel. Stenosis of 60 per cent was found in the mid-left anterior descending artery, with a small but otherwise normal distal vessel. There was extensive disease in the circumflex system, with proximal stenoses of 90 per cent and distal disease in the second obtuse marginal artery and stenosis of 70 per cent in the continuing atrioventricular groove branch.

On a medical programme the patient continued to have stable class II angina. At follow-up evaluation in 1979, an electrocardiogram showed normal sinus rhythm with non-specific repolarisation abnormalities. The serum cholesterol level was 7.42 mmol/l (287 mg/100 ml) and the serum triglyceride level was 1.26 mmol/l (102 mg/100 ml), with an increase in low density lipoproteins and a pattern consistent with type II hyperlipidaemia. A treadmill exercise test was positive, with the onset of angina at 4.3 minutes of exercise at a heart rate of 145 beats/min and subsequent 3 mm anterior ST segment depression. The patient exercised for 9.3 minutes and achieved a peak heart rate of 162 beats a minute with a calculated functional aerobic capacity of 100 per cent.

Case 4

The identical twin brother of case 4 first experienced angina at the age of 47 years in 1974. Risk factors included hypertension for approximately 30 years, a 15-year history of smoking 20 cigarettes a day, and mild increase in the serum lipids. There was no history of diabetes.

The patient was first seen at the Mayo Clinic in June 1974, at which time he was 174 cm tall and weighed 76 kg. His blood pressure was 140/100 mmHg. Examination of the cardiovascular system was normal, except for a fourth heart sound. Peripheral pulses were normal. There were no stigmata of hyperlipidaemia.

The patient had a normal chest x-ray and blood sugar level. The cholesterol level was 6.83 mmol/l (264 mg/100 ml), and the serum triglyceride level was 2.95 mmol/l (238 mg/100 ml), with a lipoprotein electrophoresis pattern consistent with type IV hyperlipidaemia. An electrocardiogram showed left ventricular hypertrophy, with ST and T abnormalities, and probable inferior myocardial infarction. A treadmill exercise test was positive, with the onset of angina at 2.7 minutes of exercise and a heart rate of 140 beats/min and 2 mm ST segment depression in the lateral precordial leads.

The second twin pair was tested for red cell antigens of the ABO, Rh, Kell, Kidd, Duffy, and MN blood groups. HLA typing for all antigens recognised by WHO was also done. All typings were identical, and the statistical likelihood of monozygosity from the erythrocyte and leucocyte typings was 97 per cent.¹ The likelihood of monozygosity is supported by the cytogenetic findings of identical polymorphisms on the Q- and C-banded karyotypes.

Cardiac catheterisation showed a normal left ventricular end-diastolic pressure but an abnormal left ventriculogram with apical and posteroseptal hypokinesis (Table 2). There was a balanced coronary system. The right coronary artery was occluded and filled by collateral vessels from the circumflex artery. There was 40% stenosis of the left main coronary artery. The left anterior descending artery had proximal stenosis of 90 per cent, with a normal distal vessel. The origin of the circumflex artery had stenosis of 60 per cent with a normal distal vessel.

The patient underwent surgery, receiving grafts to the right coronary, left anterior descending, and circumflex coronary arteries. At follow-up evaluation in 1979, he was asymptomatic without angina but was taking propranolol for hypertension. An electrocardiogram showed left ventricular hypertrophy with ST and T abnormalities and abnormal depolarisation from an inferior myocardial infarction. The cholesterol level was 7.11 mmol/l (275 mg/100 ml), and the triglyceride level was 3.78 mmol/l (305 mg/100 ml), with a lipoprotein electrophoresis pattern consistent with type IV hyperlipidaemia. Results of a treadmill exercise test were abnormal, with an increase in ST and T abnormalities during exercise. The patient was asymptomatic with this and was able to exercise for nine minutes and achieve a maximal heart rate of 143 beats/min with a functional aerobic capacity of 100 per cent.

Discussion

Inherent in all studies on the development of coronary atherosclerosis is the problem of distinguishing between environmental and hereditary factors. Prospective studies of large cohorts of twins in the Danish and the Swedish National Twin Registry have shown that there is a greater degree of concordance for coronary heart disease among monozygotic twins than among dizygotic twins.²⁻⁵ Previous case reports of identical twins with coronary artery disease are limited.⁶⁻¹¹ Some of these reports lack documentation of genetics, while others lack documentation of the disease. There

has been only one previous report in which selective coronary arteriography was performed in a twin pair.¹¹ Two additional studies documented the coronary artery disease with a non-selective aortic root flush technique.^{8 10}

The twin pairs reported herein are identical, as shown by their physical appearance, blood groups, and identical chromosomal polymorphisms (Table 1). In each pair the onset of symptoms occurred at much the same time, as has been true for other twins with coronary artery disease.^{6 11} Similar risk factors were present in each, including identical environment, smoking, and hyperlipidaemia in the first pair, and identical environment, hypertension, and hyperlipidaemia in the second. Neither pair gave a history of any significant alcohol use that would have accounted for the hyperlipidaemia. In the first pair, there were no abnormalities of the plasma lipid levels in the other relatives who were tested, including the older brother, who had had coronary artery surgery, and the four children of case 2. In this pair, the twin with the most severe disease (case 2) also suffered from labile hypertension and obesity.

Similarities in the baseline electrocardiogram and in exercise testing, specifically work load, angina threshold, electrocardiographic changes, and rapid recovery, were striking, reflecting similar cardiovascular responses to exercise and limitation by the coronary artery disease. Similarities in coronary artery disease also were striking within each pair—the first pair having severe disease with a dominant right coronary artery and involvement of both left anterior descending and circumflex coronary arteries. In the second pair, one patient had a dominant left circulation and the other had a balanced circulation. One (case 4) had more severe proximal coronary artery disease with adequate distal vessels for the surgical approach, but the other (case 3) also had disease involving the three major arterial trees. This similarity in location and extent of disease also has been documented in the twin pairs described previously by Kreulen *et al.*¹¹

A unique blend of factors results in the development of coronary artery disease in any given person. Subtle differences from patient to patient may be responsible for the great variety in pathological lesions and clinical course. The twins we describe share common risk factors, environment, and heredity. Other reports of twins^{10 11} with coronary artery disease have included non-twin family

members with identical lipid abnormalities and environments without symptomatic clinical coronary artery disease, so that neither the hyperlipidaemia nor the environment *per se* may have been a major causative factor for the pairs we described. Though this report by itself does not have statistical value in determining how hereditary and environmental factors interact in causing coronary artery disease, the remarkable similarities in clinical presentation, response to exercise, and pathological anatomy may be best explained on the basis of identical heredity. The additional risk factors of obesity, labile hypertension, and smoking may modify the genetic susceptibility and may be responsible for the inter-twin differences in the severity of the disease.

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