

Relationship between corneal arcus and hyperlipidaemia is clarified by studies in familial hypercholesterolaemia

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SUMMARY In subjects with familial hypercholesterolaemia for whom integrated exposure to hyperlipoproteinaemia can be determined, arcus development correlates with age rather than extent or pattern of hyperlipoproteinaemia. This permissive effect whereby arcus development becomes progressively time-dependent rather than dose-dependent at increasing levels of hyperlipoproteinaemia may underlie difficulties in the interpretation of premature corneal arcus in less specific disorders. Arcus development is not apparently influenced by levels of high-density lipoprotein in plasma.

Patients with premature corneal arcus may be hyperlipidaemic. However, it is the common experience that patients selected because of either hyperlipidaemia or accelerated corneal arcus do not show any obvious association between the extent of these 2 disorders. A probable reason for this discrepancy is that most patients with hyperlipidaemias do not have primary disorders, nonfamilial type IIa and IIb disorders being the most common finding.¹⁻³ These secondary hyperlipidaemias may fluctuate in extent and are very unlikely to have been present from early life. Thus the extent and duration of the hyperlipidaemia prior to assessment cannot be estimated, only the extent at the time of analysis. Furthermore, there is no clear evidence in man that regression of corneal arcus is achieved by control of any associated hyperlipidaemia, further obscuring any general relationship with a fluctuating or intermittent hyperlipidaemia.

In attempting to define any such general relationship, forms of familial hypercholesterolaemia (FH) are of special interest. Accelerated development of corneal arcus is common and in these disorders the plasma lipoprotein patterns are broadly consistent from early life until diagnosis and treatment, irrespective of age.^{4,5} Thus integrated exposure to hyperlipidaemia and to levels of specific lipoprotein components in plasma can be calculated, and possible

associations with the development of corneal arcus can then be assessed.

Clinical and biochemical observations were recorded for patients homozygous and heterozygous for FH. The extent of corneal arcus was assessed on a graded scale, and the relationship with extent and pattern of dyslipoproteinaemia was assessed mainly from data recorded for new heterozygotes seen at presentation before treatment.

Patients and methods

SELECTION OF PATIENTS

Nineteen male and 8 female heterozygotes were identified and assessed on presentation over a 4-year period at the Lipid Clinic of St Bartholomew's Hospital. Diagnosis was made from symptoms and signs at presentation, lipoprotein profiles, and family studies, with some exclusion of other causes of hyperlipoproteinaemia. Studies of cell-surface receptors for low-density lipoprotein (LDL) were not regularly performed. Observations recorded are shown in Tables 1 and 2. Corneal arcus or xanthelasmata had led to presentation of some cases, but many asymptomatic cases were diagnosed through family studies and no selection bias other than survival was apparent.

The six homozygotes seen were attending the Hammersmith Hospital, London, for plasma exchange. Diagnosis had been previously established,

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Table 1 *Heterozygous familial hypercholesterolaemia: male patients assessed at presentation, before treatment*

No.	Age seen	Presentation	Arcus grade	Xanthelasma	Xanthoma
1	42.0	Large xanthelasma for 18 months	1	+	0
2	31.2	Screen in affected family: asymptomatic	2	0	++
3	22.9	Arcus noted age 22.6 by general practitioner	3	0	0
					+age 24.1
4	40.4	Incidental: investigation of headaches	1	+	+
5	53.5	Investigation of tinnitus and deafness	1	0	+
6	27.6	Arcus seen on removal of corneal foreign body	2	0	++
7	48.2	Xanthelasmata for 3 years	1	+	0
8	23.10	Screen in affected family: asymptomatic	0	0	+
9	31.1	Investigation of chest pain age 30.9: heart normal	1	0	0
					+age 34.3
10	17.9	Screen in affected family: asymptomatic	0	0	0
11	37.0	Investigation of chest pain age 36: hiatus hernia found	2	0	0
12	23.2	Screen in affected family: asymptomatic	0	0	++
13	50.6	Large xanthelasmata age 50	3	+	++
14	45.1	Lipaemia at executive screen: asymptomatic	1	0	+
15	39.0	Small xanthelasma age 33: asymptomatic	1	+	+
16	69.0	Screen in affected family: asymptomatic	4	0	++
17	11.4	Screen in affected family: asymptomatic	1	0	0
18	48.1	Xanthelasmata for 18 months	3+	+	+
19	51.10	Routine investigation at surgery for acute jejunal stricture age 50.9. MI age 40	2	0	+

LBBB=left bundle branch block. C=cholesterol. MI=myocardial infarct. TG=triglycerides. Xanthoma: ++ indicates lesions at 2 independent sites—e.g., hands and heels.

and various other studies of some of these rare patients have been published.⁶⁻⁹ Heterozygotes numbers 26 and 27 are twins, presumed nonidentical; 10, 12, and 20 are siblings, and 16 is the father of 15. The homozygotes are unrelated to the heterozygotes or to each other, and observations are shown in Table 3.

CLINICAL ASSESSMENT

Full general and ophthalmological examination was performed by the author. The degree of arcus was evaluated, using a hand-held ophthalmoscope on a scale of 0-4 similar to previous methods^{10 11}: grade 1, upper or lower segment arcus; grade 2, both segments

affected; grade 3, both segments and just confluent; grade 4, heavy confluent arcus.

Various cardiovascular assessments were also performed. All heterozygotes had fasting levels of glucose in plasma within the normal range and were not hypertensive.

BIOCHEMICAL ASSESSMENT

Fasting lipoprotein profiles were obtained for new heterozygotes on at least 2 occasions, average values being cited. Levels of total high-density lipoprotein (HDL) cholesterol in plasma were also obtained for some patients by the manganese chloride/heparin

Table 2 *Heterozygous familial hypercholesterolaemia: female patients assessed at presentation, before treatment*

No.	Age seen	Presentation	Arcus grade	Xanthelasma	Xanthoma
20	25.3	Screen in affected family: asymptomatic	1	0	+
21	54.2	Investigated as strong family history of premature heart disease: asymptomatic	2+	0	+
22	34.2	Arcus noted by optician	3	0	+
23	19.10	Screen in affected family: asymptomatic	0	0	0
24	58.2	Bilateral xanthelasmata noticed age 58	2	+	+
25	57.6	Investigation of progressive tinnitus and deafness	4	0	+
26	51.2	Screen in affected family: asymptomatic twins	3	0	+
27	51.2	Screen in affected family:	3	0	+

Cases 26 and 27 are bracketed because they are twins.

Cardiac chaemia	Fasting plasma lipids mmol/l				Ratio HDL/LDL	TG×age	Chol×age	LDLC×age
	TG	Chol	HDLC	LDLC				
	2.2(3)	9.6(3)	0.91	7.68	0.119	92.4	403	322.5
	3.0(3)	10.4(3)	0.90	8.12	0.111	93.5	324	253
	1.05(4)	9.0(4)				23.9	205	
.BBB age 40.4	2.4(3)	8.3(3)				97.0	335	
AI age 42	1.6(3)	9.0(3)	1.27	6.99	0.182	85.5	481	373.5
	1.12(3)	11.4(3)	1.20	9.28	0.129	30.8	302.5	255
	2.45(7)	7.4(7)	0.75	5.52	0.136	118	356.5	266
	2.4(4)	13.9(4)	0.97	11.83	0.082	57.2	331	282
	0.86(4)	9.6(4)	1.32	7.88	0.168	26.7	298.5	245
	1.8(1)	8.8(1)				32.0	156	
	1.4(5)	8.0(5)	1.36	6.00	0.227	51.2	296	222
	1.5(3)	10.5(3)	1.30	8.51	0.153	34.7	243	197
AI×3 from age 42	3.7(3)	11.8(3)	0.77	9.33	0.083	187	596	471
	3.9(3)	10.1(3)				176	455.5	
	1.03(2)	10.4(3)				40.2	405.5	
	1.2(1)	8.5(3)	1.22	6.73	0.181	82.8	586.5	464
	0.55(2)	8.4(3)	1.50	6.65	0.226	6.2	95.2	75.3
	2.68(3)	9.9(3)				129	476	
AI age 40	1.8(2)	8.1(1)				92.9	420.4	

procedure. Levels of LDL cholesterol were then calculated.¹² Data were available for homozygotes before and during treatment. Partial reduction in levels of cholesterol in plasma had been achieved with homozygous patients B, D, and F by plasma exchange for periods of approximately 1, 2, and 3 years, plus a brief further reduction in patient B achieved by a portocaval shunt. These minor responses were well documented and it was possible therefore to calculate corrected integrated exposure (see below) as shown in Table 3. Lipoprotein values cited were not recorded within 3 months of an episode of acute myocardial ischaemia to avoid artefactual results.

EVALUATION OF DATA

Clinical and biochemical data recorded for the 19 male and 8 female heterozygotes assessed at presentation were subjected to multivariate analysis by the SPSS programme, determining intervariable correlation coefficients and their levels of significance for each group and for both groups combined. The derived terms additionally incorporating age represent integrated exposure at assessment. Thus a patient presenting at age 27.5 years with an average level of total cholesterol in plasma of 10 mM has an integrated exposure for total cholesterol of 275 units.

Cardiac schaemia	Fasting plasma lipids mmol/l				Ratio HDL/LDL	TG×age	Chol×age	LDLC×age
	TG	Chol(C)	HDLC	LDLC				
)	1.3(3)	9.5(3)	1.17	7.73	0.151	32.8	240	195
)	1.5(3)	8.0(3)				81.2	433.5	
)	1.35(2)	9.7(2)	2.1	6.98	0.301	46.1	331.5	238.5
)	1.35(3)	8.1(3)	1.26	6.22	0.203	26.8	160.5	123.5
)	2.4(3)	10.3(3)				139.5	599	
)	1.13(3)	11.2(3)	2.54/12.4	9.22	0.275	65.0	644	530
)	1.25(3)	8.35(4)	1.3	6.48	0.200	64	427	331.5
)	1.45(3)	9.3(3)	1.25	7.38	0.169	74.2	476	378

Table 3 Homozygous familial hypercholesterolaemia. Data on 6 patients showing arcus grade at age of assessment and fasting plasma lipids with integrated exposure to hypercholesterolaemia, after correction for short-term responses to treatment with patients B, D, and F

Patient	Age/sex	Arcus grade	Xanthelasma	Xanthoma	Cardiac status	Chol mmol/l	TG mmol/l	Chol×age
A	5.3 F	1	0	++	Aortic stenosis, silent coronary occlusion	23.6	1.19	126
B	28.9 F	0	0	+	Aortic stenosis, CAVBG×3	16.1-11.4	2.0	461.5
C	15.3 M	2	0	++	Aortic stenosis	19.8	1.8	287
D	16.5 M	2	0	++	Aortic stenosis, ostial narrowing	20.1-8.4	1.07	280
E	19.5 M	1/2	+	++	Aortic stenosis CAVBG	18.0	1.85	344
F	26.7 M	3	0	++	Silent MI age 22	15.5-8.7	0.9	385

Levels of HDL in plasma were depressed in all patients. Patient E showed unequal development of arcus. CAVBG=coronary artery vein bypass graft.

Variables and the total number of values recorded were:

age of patient	(27)
arcus grade	(27)
cholesterol	(27)
triglycerides	(27)
HDL cholesterol	(18)
LDL cholesterol	(17)
HDL/LDL chol. ratio	(18)
triglycerides×age	(27)
cholesterol×age	(27)
HDL chol.×age	(18)
LDL chol.×age	(17)
HDL/LDL chol. ratio×age	(18)

A mean value for LDL cholesterol is not given for patient 25 in view of sample variation, but values for HDL cholesterol and HDL/LDL cholesterol ratio for a specific sample are cited.

Results

In the multivariate analysis it was assumed that arcus grade could be used as both a discrete and continuous variable, and analysis of the combined data for new heterozygotes supported a linear trend of arcus grade with age by means of a one-way analysis of variance with contrasts. Mean age of patients and numbers for each arcus grade were as follows:

Grade 0	21.1 years (4)
Grade 1	37.3 years (9)
Grade 2	43.2 years (6)
Grade 3	43.0 years (6)
Grade 4	63.3 years (2)

Analysis indicated a clear positive correlation between arcus grade and age for the 19 male heterozygotes ($r=0.535$, $s=0.009$), the 8 females ($r=0.724$, $p=0.021$) and for all 27 heterozygotes combined ($r=0.616$, $s=0.001$).

This correlation may be expressed as a linear relationship, shown with calculated regression lines for the combined group and for males only in Fig. 1.

CORNEAL ARCUS AND PATTERNS OF DYSLIPOPROTEINAEMIA

Significant correlations were not obtained between arcus grade and plasma triglycerides or total cholesterol, LDL cholesterol, or with the HDL/LDL cholesterol ratio (limited data were available). Correlations were obtained with these values and with HDL cholesterol as integrated terms additionally

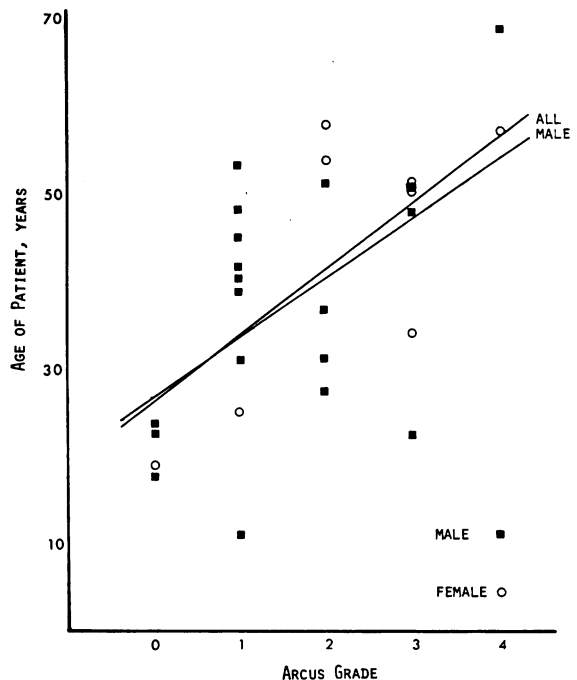


Fig. 1 Corneal arcus and familial hypercholesterolaemia. Relationship between age and arcus grade for heterozygotes at presentation. Regression lines were derived for: All patients: $age=26.19+7.59$ arcus grade. Males only: $age=26.96+6.91$ arcus grade.

incorporating age, but these were invalid in view of the correlation with age alone. However, the relationship between arcus grade and (plasma cholesterol \times age) is of interest, as data for the 6 homozygotes may be included after correction for minor responses to treatment as shown in Table 3. This relationship is shown in Fig. 2, with the regression lines for heterozygotes to which the additional data also broadly conform.

A moderate positive correlation between arcus grade and HDL cholesterol with the combined group of heterozygotes ($r=0.420$, $p=0.041$) was not found with the male and female patients alone, the non-significant correlation for males being negative.

Discussion

A general relationship between age of patient and extent of corneal arcus is widely recognised, but factors influencing the development of corneal arcus are clarified in the extreme case of familial hypercholesterolaemia. Development is related to the patients' age and thus to the duration of hyperlipoproteinaemia, rather than to its extent or pattern, over a wide range of exposure.

The overriding relationship with age is consistent with a permissive effect and a saturation process, becoming progressively time-dependent rather than dose-dependent with increasing hyperlipidaemia and particularly with excess of low-density lipoprotein. This indirect relationship probably contributes to the more general problem of assessment of the clinical significance of corneal arcus in patients with a background of hyperlipidaemia, which is less specific or consistent than with monogenic familial hypercholesterolaemia. An added complication is that arcus is a cumulative process which is not known to regress in man, and appears to be unaffected by reduction in level of any associated hyperlipidaemia. Further racial and local factors above this permissive effect may contribute to the observed wide individual variation, including differential carotid stenosis, as with homozygous patient E, local corneal temperature and limbal blood flow, and secondary changes in long-standing insudated deposit, which impair remobilisation.^{9,13}

The level of HDL in plasma is a negative risk factor for ischaemic heart disease. Limited data in the present study suggest that levels of HDL in plasma or the HDL/LDL cholesterol ratio do not significantly influence arcus development. The same data have also shown that the development of xanthelasmata, in which lipid deposits are intracellular in contrast to those of corneal arcus, are promoted by hypertriglyceridaemia and relative deficiency of HDL,⁹ although the 2 factors are not independent. These observations further reinforce the dissociation between cardiovascular disease and arcus development.

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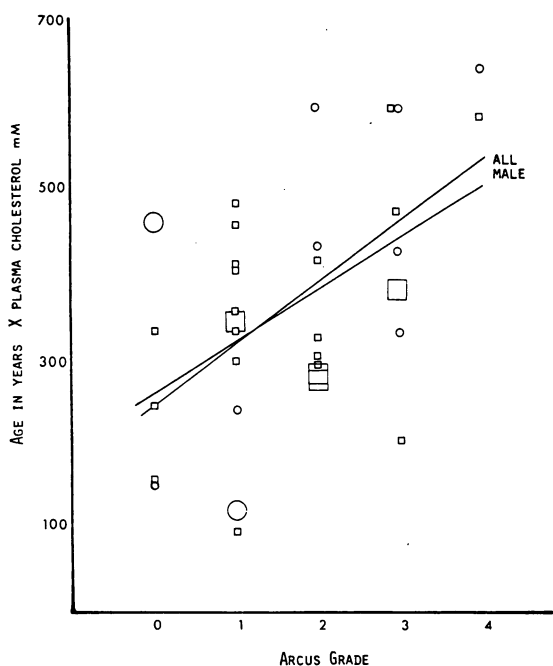


Fig. 2 Corneal arcus and familial hypercholesterolaemia. Arcus grade and age \times plasma cholesterol for heterozygotes at presentation and for homozygotes—large points—on treatment. Males, square points; females, circles. Regression times for heterozygotes were derived for: All patients: age \times chol. = $245.02 + 73.55$ arcus grade. Males only: age \times chol. = $264.33 + 59.98$ arcus grade.

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