CLINICAL RESEARCH

Improved survival of patients with homozygous familial hypercholesterolaemia treated with plasma exchange

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Abstract

Plasma exchange was undertaken in five patients with homozygous familial hypercholesterolaemia at intervals of two weeks for a mean of 8.4 years. These patients had survived an average of 5.5 years longer than their five respective homozygous siblings ($p = 0.03$), each of whom must have had a matching genetic defect but who died untreated. The 37% decrease in peak serum cholesterol concentrations maintained by plasma exchange presumably reduced progression of atherosclerosis in the treated patients and thus lessened their risk of premature death.

Introduction

The use of plasma exchange to treat homozygous familial hypercholesterolaemia was first introduced 10 years ago.¹ Familial hypercholesterolaemia can be caused by any one of the seven described mutations of the gene for the low density lipoprotein receptor² that has recently been cloned.³ Inheritance of identical or dissimilar mutant alleles from each parent gives rise to the homozygous form of the disease, which is characterised by a considerable increase in low density lipoprotein cholesterol concentration from birth, appearance of cutaneous xanthomas and onset of aortocoronary atherosclerosis in childhood, and a liability to sudden death in early adult life.⁴

Familial hypercholesterolaemia is notoriously resistant to treatment with diet and drugs, although receptor defective homo-

zygotes, who have detectable low density lipoprotein receptor activities, respond better than receptor negative homozygotes, in whom such activities are absent.^{4,5} These differences reflect the nature of the underlying mutation and result in considerable variability between homozygotes with respect to the speed of onset of cardiovascular complications⁶ and age at death.⁴ This paper reports the beneficial effects of plasma exchange on the survival of five homozygotes treated after 1975, each of whom had a homozygous sibling, with a presumed identical defect of low density lipoprotein receptor, who died without undergoing this treatment.

Subjects and methods

All five patients have been described in detail previously.⁷⁻⁹ Two (cases 1 and 2) were treated after 1975-6 at Hammersmith Hospital, London; one (case 3) was treated in London 1978-80 but afterwards at the Manchester Royal Infirmary; and two (cases 4 and 5) were treated from 1976 onwards at the Children's Hospital, Boston. Plasma exchange was performed roughly every two weeks on an outpatient basis using an Aminco or IBM continuous flow cell separator, with 2.5-5 l plasma protein fraction as the exchange medium and heparin as the anticoagulant.¹ Serum cholesterol and triglyceride concentrations were measured immediately before each plasma exchange, either by colorimetric methods⁷⁻⁹ or latterly by enzymatic analysis (Technicon autoanalyser methods No SE4-0065 FBI and SE4-0039 PE6). High density lipoprotein cholesterol concentration was measured similarly, after heparin-manganese precipitation.¹⁰ Low density lipoprotein receptor state was determined in cultured skin fibroblasts.¹¹

Details of each patient's age, biochemical state, and duration of plasma exchange are given below, but additional information is as follows: an Englishman (case 1) died in 1984 after a failed aortic valve replacement procedure. In addition to plasma exchange, he had received nicotinic acid 5 g/day and, latterly, mevinolin 80 mg/day. Another Englishman (case 2) also received nicotinic acid and, more recently, mevinolin 80 mg/day. He underwent prophylactic coronary artery bypass grafting in 1983 and remained asymptomatic. An Asian man (case 3) lived in Britain but went home to Zambia for two months each year, during which time he did not undergo plasma exchange. He recently underwent prophylactic coronary artery bypass grafting for his angiographically documented but asymptomatic coronary ostial stenosis. An American man (case 4) underwent partial ileal bypass aged 17,⁹ which was reversed one year later due to gastrointestinal side effects. An American woman (case 5) underwent total biliary diversion aged 6 without benefit⁹; biliary continuity was restored 21 months later. The four living patients remained well and continued treatment with plasma exchange.

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Results

Table I shows the low density lipoprotein receptor state and basal serum lipid concentrations in the five homozygotes who underwent plasma exchange. One patient (case 5) was receptor negative, the four others receptor defective. All had severe hypercholesterolaemia, which, in the presence of normal triglyceride and subnormal high density lipoprotein cholesterol concentrations, can be calculated as being due to roughly fourfold increase in low density lipoprotein cholesterol concentrations.¹²

Table II shows details of the age and sex of these patients and their homozygous siblings, together with the duration and cholesterol lowering effect of plasma exchange. This procedure has been performed for the past nine years in four patients and for six years in the remaining patient (case 3).

TABLE I—Low density lipoprotein receptor state and serum lipid concentrations (mmol/l) before treatment in five homozygotes with familial hypercholesterolaemia

Case No	Receptor state	Serum cholesterol	Triglyceride	High density lipoprotein cholesterol
1	Defective	19.6	0.90	0.72
2	Defective	19.8	1.10	0.65
3	Defective	18.0	0.90	0.85
4	Defective	19.0	2.71	0.67
5	Negative	17.9	0.73	0.72

Conversion: SI to traditional units—Cholesterol: 1 mmol/l $\approx$ 38.6 mg/100 ml. Triglyceride: 1 mmol/l $\approx$ 88.5 mg/100 ml.

between fortnightly exchanges.¹⁷ As a result total and low density lipoprotein cholesterol concentrations in homozygotes undergoing this treatment are similar to those found in untreated heterozygotes with familial hypercholesterolaemia.

The defect of low density lipoprotein receptor responsible for familial hypercholesterolaemia was first identified in 1973 by Goldstein and Brown,²³ and they and their colleagues have subsequently investigated in detail the structure and function of the low density lipoprotein receptor and its gene.³ Their findings indicate that several different mutations exist, any one of which can give rise to the phenotype of familial hypercholesterolaemia. Biochemical expression of the disorder depends on the nature of the underlying mutation. Fibroblasts from receptor negative homozygotes, for example, express virtually no detectable low density lipoprotein receptor activity, whereas receptor defective homozygotes can express 25-30% of the activity seen in normal fibroblasts.^{4,5} Receptor negative homozygotes seem to have mutations that prevent synthesis or maturation of the low density lipoprotein receptor.² Clinical severity, judged by degree of hypercholesterolaemia, earliness of onset of cardiovascular complications, unresponsiveness to treatment with drugs, and liability to premature death, is also more noticeable in receptor negative than in receptor defective homozygotes.^{4,6,24}

The variability of expression of homozygous familial hypercholesterolaemia resulting from genetic heterogeneity can be overcome by using pairs of siblings as, by definition, each homozygous

TABLE II—Ages of homozygotes with familial hypercholesterolaemia undergoing plasma exchange and of their untreated homozygous siblings

Case No	Sex	Age (years)	Plasma exchange		
			Duration (years)	Mean (SD) cholesterol pre-exchange (mmol/l)	Age when treatment began (years)
1	M	31.7*	9	11.5 (1.0)	22
Sibling	F	19.4*			
2	M	22.0	9	12.2 (1.7)	13
Sibling	M	17.2*			
3	M	21.0	6	11.8 (1.8)	14
Sibling	M	23.3*			
4	M	22.8	9	11.6 (1.0)	14
Sibling	M	14.5*			
5	F	18.5	9	11.9 (1.0)	9
Sibling	M	13.9*			

*Deceased.

Conversion: SI to traditional units—Cholesterol: 1 mmol/l $\approx$ 38.6 mg/100 ml.

Reduction in serum cholesterol concentrations ranged from 34-41%, being least in the receptor negative patient (case 5).

Table II also shows the age of death of the untreated homozygotes and age at which plasma exchange was begun in their siblings. Three sibling pairs were all male, two were mixed. All but one of the treated patients are still alive, and he (case 1) died postoperatively, whereas all their untreated homozygous siblings are deceased. In each instance death of siblings was sudden and due to atherosclerosis, as described previously.^{8,9} All but one of the treated patients survived longer than their respective siblings, the mean difference in life span being 5.5 years. Application of the paired log rank test shows that this difference is significant (one tailed, $p = 0.03$).¹³

Discussion

Plasma exchange has been used to treat homozygous familial hypercholesterolaemia in several centres during the past 10 years.^{1,9,14-16} The safety and beneficial effects of this procedure in 13 such patients were reviewed four years ago,¹⁷ and thereafter further reports have appeared.^{18,20} Regression of cutaneous and tendinous xanthomas is well documented, and there is evidence that this is usually,^{12,21} but not always,²² accompanied by a reduced rate of progression of aortocoronary lesions. Serum cholesterol concentrations measured immediately before plasma exchange, when they are at their highest, are 40% lower than with conventional treatment, which represents a 50% reduction in the mean plasma concentration

sibling is bound to have inherited the same pair of mutant alleles from their heterozygous parents. Measurement of low density lipoprotein receptor activity in siblings confirms the validity of this assumption.⁵ Differences of sex seem less important in determining the onset of cardiovascular complications in homozygotes²⁵ than in heterozygotes,²⁶⁻²⁸ and receptor state seems to be the overriding factor. High density lipoprotein cholesterol concentrations were subnormal in all five homozygotes before plasma exchange was initiated, which is common.⁴ Four of the five patients underwent surgical procedures, but probably none of these was operative for long enough to have influenced prognosis.

Although the numbers were small, the duration of treatment was sufficiently long to show that plasma exchange significantly improves life expectancy in homozygous familial hypercholesterolaemia. The beneficial effect of this procedure may have been enhanced by concomitant administration of lipid lowering drugs, notably nicotinic acid and more recently mevinolin.²⁹ The latter in a dose of 80 mg/day resulted in a further 11.5% reduction in serum cholesterol concentration before exchange compared with that in plasma exchange alone (unpublished data). The net result was a halving of low density lipoprotein cholesterol concentrations, which presumably was the chief reason for the clinical improvement and stabilisation of atherosclerotic lesions documented previously.⁷

Plasma exchange also reduces plasma fibrinogen concentrations, platelet counts, and high density lipoprotein cholesterol concentra-

tions, but these all return to normal within a week,¹⁻³⁰ whereas low density lipoprotein cholesterol concentrations rise again more slowly. Whether procedures designed to selectively remove low density lipoprotein but conserve high density lipoprotein and other proteins will prove to be as or more effective than plasma exchange remains to be shown.³¹⁻³³ Transplantation of the liver provides the most definitive approach to treatment currently available but necessitates long term immunosuppression, with its attendant drawbacks.³⁴⁻³⁵ We conclude that plasma exchange every two weeks offers a safe and proved means of improving prognosis in homozygous familial hypercholesterolaemia with which all newer forms of treatment can be compared.

We thank all our colleagues, both doctors and nurses, whose skill and stamina have enabled well over 1000 plasma exchanges to be undertaken over the past 10 years without mishap, Drs J Goldstein and M Brown for measuring the low density lipoprotein receptor state of fibroblasts from the three patients treated in Britain, and Dr R Peto and Mr D Robinson for undertaking the statistical analysis.

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Emphysema, cirrhosis, and heart block in a young patient with partial α_1 antitrypsin deficiency (PiMZ phenotype)

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Abstract

Severe lung disease and liver disease are not recognised features of the PiMZ phenotype, which is associated with α_1 antitrypsin deficiency. A 31 year old woman with this phenotype was found to have emphysema and complete heart block and showed evidence

of hepatic cirrhosis, although her three sisters, all of whom had the same phenotype, were clinically normal.

This case supports the possibility of a causal relation between the PiMZ phenotype and chronic lung and liver disease, but an association between α_1 antitrypsin deficiency and complete heart block could not be proved in this patient.

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Introduction

It is not clear whether the α_1 antitrypsin PiMZ heterozygous state predisposes to lung disease.¹⁻⁴ We report on a patient with the PiMZ phenotype who at the age of 36 had severe emphysema, evidence of hepatic cirrhosis, and complete heart block. Neither severe lung disease nor liver disease is a recognised feature of the PiMZ phenotype, and heart block has not previously been reported in association with partial α_1 antitrypsin deficiency.