

# Long-term prevention of premature coronary atherosclerosis in homozygous familial hypercholesterolemia

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Homozygous familial hypercholesterolemia (FHH) leads to severe premature atherosclerosis. A 22-year-old woman with FHH has been treated with a combination of H.E.L.P. apheresis (heparin-mediated extracorporeal LDL precipitation) and statins for 15 years. The combined treatment maintained a plasma LDL-cholesterol reduction from baseline of 840 to 122 mg/dL (85% reduction). In addition, H.E.L.P. apheresis reduced the elevated lipoprotein(a) and fibrinogen levels by 60% to 70%. All xanthomata disappeared. There is no evidence of premature atherosclerosis studied by means of electron beam computed tomography and <sup>15</sup>N-ammonia positron emission tomography: The entire coronary vasculature is free of calcifications. Her myocardial blood flow at rest (87 mL/100 g/min) and during stress (308 mL/100 g/min) and the coronary flow reserve (3.5) are normal after H.E.L.P. treatment. This case demonstrates the efficacy and safety of the combined treatment of H.E.L.P. apheresis and statins even in serious cases of FHH. (J Pediatr 2002;141:125-8)

Homozygous familial hypercholesterolemia (FHH) represents a potentially fatal condition that is caused by >90% low density lipoprotein cholesterol (LDLC) receptor deficiency. Treatment of FHH requires drastic, life-long reduction of plasma cholesterol, beginning as early as possible. Untreated, severe atherosclerosis develops during childhood, and children with this disease may die of heart attacks or aortic stenoses caused by valvular cholesterol deposits.<sup>1</sup>

Statins alone are not effective in FHH. Because successful gene therapy is not available, the alternatives to treat FHH are organ transplantation (liver, heart) or regular plasma exchange. Plasma exchange has been shown to prolong life.<sup>1,2</sup> In recent years, plasma exchange has been replaced by more selective LDLC apheresis systems, one of which is heparin-mediated extracorporeal LDLC/fibrinogen-precipitation (H.E.L.P.) apheresis.<sup>1-3</sup>

We report a case (the first world-wide to receive continuous treatment) of a 22-year-old woman with FHH who received continuous treatment of H.E.L.P. apheresis in combination with statins throughout a 15-year period.

## HISTORY

The patient was diagnosed with FHH at 2 years of age: total cholesterol was 9.4 g/L and LDLC, 820 mg/dL. When the patient was 6 years old, the total cholesterol concentration peaked at 10.5 g/L despite a strict low-fat diet and cholestyramine, which at the time was the only available treatment. Her residual LDLC receptor activity was 7% to 10%. She had xanthomata around the eyes, wrists, elbows, ankles, and both

EBCT	Electron beam computed tomography
FHH	Homozygous familial hypercholesterolemia
HDLC	High density lipoprotein cholesterol
H.E.L.P.	Heparin-mediated extracorporeal LDL/fibrinogen-precipitation
LDLC	Low density lipoprotein cholesterol
MBF	Myocardial blood flow
PET	Positron emission tomography

thighs and had been hospitalized for angina. The angina was probably of microcirculatory origin; myocardial infarction was excluded by electrocardiographic monitoring and the respective enzyme pattern.

Her parents and first cousins all had heterozygous FH. Her father died at 32 years of age and her paternal uncle at 31 years of age of myocardial infarction.

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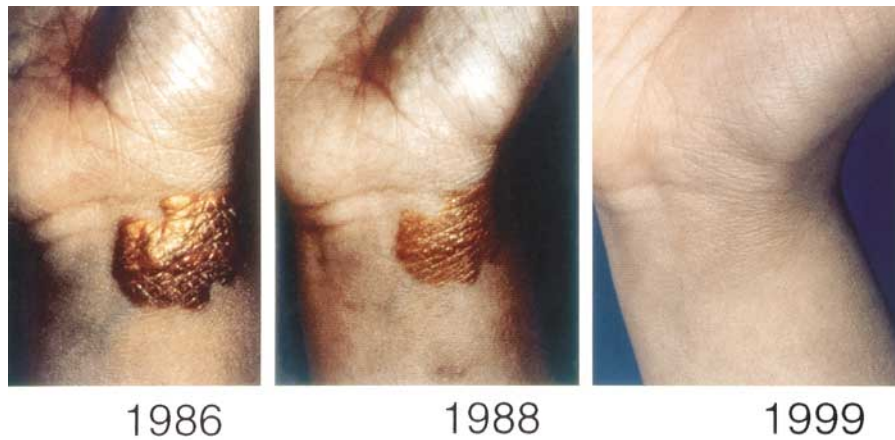
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**Figure.** Regression of xanthomata under HELP-apheresis treatment. View of the patient's right wrist.

**Table I.** Effects of H.E.L.P. apheresis on myocardial perfusion studied with <sup>13</sup>N-ammonia rest/stress PET

	PET before apheresis	PET after apheresis
LDLC (mg/dL)	204	39
Fibrinogen (μmol/L)	8.76	1.5
Pulse (min <sup>-1</sup> )	98	95
Blood pressure (mm Hg)	118/74	118/75
MBF at rest (mL/100 g/min)	1024 ± 244	871 ± 113
MBF at stress (mL/100 g/min)	2598 ± 760	3084 ± 527
Coronary flow reserve	2.571	3.554

The first PET study was performed in the morning before the apheresis, the second PET study the next morning. Both PET studies were performed according to the same protocol. MBF during stress, that is, after infusion of adenosine to induce maximal vasodilation, divided by MBF during rest describes the coronary flow reserve. Coronary flow reserve is a measure for the ability to adapt to physical stress. The increase in coronary flow reserve after H.E.L.P. apheresis is significant ( $P < .05$ ).

Her mother was symptomless, but two maternal cousins also died of myocardial infarction at 14 and 18 years of age.

## TREATMENT

Initial reports of the successful use of plasmapheresis in FHH<sup>1,2</sup> suggested the application of H.E.L.P. apheresis (B. Braun AG, Melsungen, Germany) because this treatment can reduce the levels of the atherogenic plasma compounds without eliminating immunoglobulins, albumin, and high density lipoprotein cholesterol (HDL).<sup>3-6</sup>

From 1986 on, the patient was treated weekly with H.E.L.P. apheresis,

which lowered the plasma LDLC levels from 840 to 240 mg/dL without any adverse effects. The xanthomas disappeared (Figure). As she grew older, her increased plasma volume permitted more intensive treatments (1-2.5 L, finally 3 L plasma volume). Average LDLC levels were maintained at 170 mg/dL. HDLC increased from 15 (1986) to 40 mg/dL (1999). Continual treatment reduced the excessive plasma fibrinogen and lipoprotein (a) levels by 60% to 70% to normal levels. When she was 11 years old, a cimino-fistula was applied to facilitate repeated venipuncture and is still in use.

In 1988, the new availability of statins permitted the addition of a daily dose of

20 mg lovastatin, which further lowered LDLC by 20%. In 1992, lovastatin was replaced by 20 mg/d simvastatin. Subsequently, simvastatin was replaced by 40 mg/d atorvastatin (1997), which lowered LDLC to an average of 122 mg/dL.

The monitoring of her physiologic development elucidated the following: onset of puberty with menarche at age 13 was entirely normal; she had a transient vitamin D deficiency that was adjusted by vitamin D supplements; liver and pancreatic enzymes, creatinine, urea, creatine kinase, uric acid, thyroid and sex hormones, albumin, immunoglobulins, hemoglobin, red and white blood cells, and platelet concentrations were within the normal ranges; there was no apparent physical or psychologic impairment. Neither apheresis nor statins caused any relevant side effects.

## RESULTS

The follow-up examination (15 years later) revealed height, 1.63 m, and weight, 50 kg. Physical examination revealed no xanthomata (Figure), no cardiac murmurs, lungs clear to auscultation, normal abdomen on palpation, and no neurologic deficits. Blood pressure was 115/70 mm Hg and pulse, 80/min.

Basic laboratory measures showed normal liver and pancreatic enzymes, except for GPT (24 U/L; range, 5-19 U/L). Total protein, albumin, immunoglobulins, CRP, ferritin, hemoglobin, red and white blood count, platelets, and differential blood count were normal, but serum iron was below the normal range: 37 μg/dL (range, 60-140). The prothrombin time and activated partial prothrombin time were normal; thyroid hormones and sex hormones were within normal ranges.

Electrocardiography showed normal PQ and QRS intervals and amplitudes; there were no ST-segment or T-wave abnormalities.

**Table II.** Acute effects of one H.E.L.P. apheresis session on plasma concentrations of lipoproteins and fibrinogen

Laboratory parameters	Cholesterol (g/L)	Triglyceride (g/L)	LDLC (mg/dL)	HDLCL (mg/dL)	Apolipoprotein		Fibrinogen (μmol/L)
					B (g/L)	(a)(μmol/L)	
Concentration before H.E.L.P.	2.52	0.79	204	15	1.64	3.25	8.76
Concentration after H.E.L.P.	0.65	0.39	39	3	0.33	0.57	1.50
Immediate reduction (%)	74	51	81	80	80	82	83
Concentration at interval	1.70	0.70	122	12	0.99	1.18	6.76

Blood samples were drawn immediately before and after treatment. Results shown were achieved by a single treatment in which 3.019 mL plasma was passed through the machine. Treatment lasted 117 minutes.  
Interval concentration describes the plasma concentration of lipoproteins and fibrinogen reached between two following H.E.L.P. sessions.

Echocardiography showed normal-sized cardiac chambers, regular wall motion, no valvular lipid deposits, and no valvar regurgitation. The fractional shortening was 0.44 with regular inner diameters and volumes of the left ventricle and an ejection fraction of 0.76. Transcranial ultrasonography showed no plaques, no calcifications, and no intimal thickening in the carotid arteries.

The electron beam computed tomography (EBCT) heart study demonstrated no calcifications of the coronary arteries (calcium score according to Agatston<sup>6</sup> = 0). There were two distinct calcifications in the aortic root (149 Hounsfield units) and 4 minimal lesions in the descending aorta (8 Hounsfield units).

The <sup>15</sup>N-ammonia rest/stress positron emission tomography (PET) study revealed normal global myocardial blood flow (MBF) at rest: 87 mL/100 g tissue per minute and 308 mL/100 g tissue per minute during stress (ie, after maximal vasodilation according to adenosine infusion<sup>7</sup>) after H.E.L.P. apheresis. In addition, coronary flow reserve was 3.5 and regional quantification of MBF for each of the epicardial arteries also was normal, reflecting a normal microcirculation.<sup>8</sup>

To evaluate whether the LDLC concentration has an influence on coronary perfusion, we examined the patient once before H.E.L.P. apheresis (high LDLC of 204 mg/dL) and again the next day after apheresis when the

concentration was reduced to 39 mg/dL. The results are shown in Table I. Of note, both studies showed no perfusion deficits, but the coronary flow reserve increased from 2.5 to 3.5 after apheresis.

As an example of the efficacy of a single apheresis session, Table II indicates the concentrations of the lipoproteins and fibrinogen before and immediately after treatment.

## DISCUSSION

This long-term follow-up report demonstrates successful prevention of coronary atherosclerosis in a patient with homozygous FH. For more than 15 years, regular treatment with H.E.L.P. apheresis in combination with statins maintained an 85% decrease of baseline plasma LDLC, enabling the patient to grow up healthy and to live a normal life. Three pieces of evidence substantiate the clinical efficacy of the treatment:

1. Clinical examination: long-term survival, freedom from coronary symptoms, no plaque formation in the carotid arteries, no restriction in physical fitness, normal electrocardiographic and ultrasonographic findings up to the age of 22 years.
2. Morphologic heart study with EBCT: The patient showed no coronary calcifications. In compar-

ison, Hoeg et al,<sup>9</sup> who had studied 24 patients with homozygous or heterozygous familial hypercholesterolemia, found massive calcifications in all patients older than 12 years despite treatment (1000-1500 Hounsfield units). The extent of calcification thereby correlated with age, severity, and duration of hypercholesterolemia and with presence and thickness of Achilles tendon xanthomata.<sup>9</sup> The difference is considerable, with the one reservation that, previously, only unselective procedures such as plasmapheresis and less potent statins were available.

3. Functional heart study with PET: Global and regional myocardial perfusion at rest and during stress and the coronary flow reserve were entirely normal. These findings suggest normal vascular reactivity of the epicardial arteries and the microcirculation, since the coronary flow reserve is impeded early in the course of atherosclerosis and before the onset of clinical symptoms.<sup>8</sup> A significant reduction of coronary flow reserve and MBF during stress is the usual constellation in FHH.<sup>10</sup> The extent of reduction depends on the severity of hypercholesterolemia.<sup>10</sup>

This can be confirmed by the PET studies showing that a reduction of

LDLC and fibrinogen by H.E.L.P. apheresis acutely improves the coronary flow reserve. Comparable results were obtained when the same protocol was applied in adults with hypercholesterolemia and coronary heart disease.

However, homozygous FH was difficult to treat. The genetic defect could neither be repaired by transplantation nor by plasma treatment. Liver or heart transplantation introduced the risk of acute or chronic rejection, unwanted immunosuppressive treatment, and considerable mortality rates. Extracorporeal apheresis systems are appropriate if they are able to eliminate LDLC and if they do not remove other essential plasma constituents such as immunoglobulins, albumin, or HDLC. Most LDLC apheresis systems do not permit concomitant use of ACE inhibitors because of bradykinin release. However, the H.E.L.P. system is fully compatible with use of these medications. Other possible side effects of every extracorporeal treatment can be problems with venipuncture, vasovagal reactions, and the rare condition of a heparin allergy.

Contrary to the observations that long-term apheresis treatment is emotionally difficult for children,<sup>1</sup> the successful treatment here appeared to have stabilizing effects on the patient and her family. She successfully graduated from high school. Unlike hemodialysis, LDLC apheresis can be handled with more flexibility regarding time (1.5- to 2-hour duration) and treatment intervals (weekly or fortnight intervals).

None of the three statins used caused a problem regarding long-term tolerability. They allowed a longer time between the apheresis sessions. However, careful monitoring is mandatory to elucidate possible effects on growth and

development. With atorvastatin, we saw a slight increase of the GPT. Apart from this and a transient vitamin D deficiency with the combined treatment, no problems were encountered.

During the last 15 years, H.E.L.P. apheresis has proven its efficacy and safety in >180,000 treatments of 1000 patients and controlled clinical studies.<sup>4,5,11,12</sup> It was approved by the US Food and Drug Administration and by the equivalent German Institution. The costs are comparable to chronic kidney dialysis therapy.

Compared with transplantation, the early and drastic reduction of the atherogenic plasma compounds by H.E.L.P. apheresis and statins offers a good therapy for children with FHH.

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