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Original Article

Impact of the characteristics of patients and their clinical management on outcomes in children with homozygous familial hypercholesterolemia

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Abstract *Objective:* To relate clinical factors to the development of cardiovascular atherosclerosis for patients with homozygous familial hypercholesterolemia. *Background:* Homozygous familial hypercholesterolemia is associated with extreme elevations in levels of cholesterol causing aggressive atherosclerosis. *Methods:* We reviewed 10 children, 8 of whom were male, assessed at a single institution. We found that individual characteristics, levels of lipid, cardiovascular investigations, and management were related to the activity of low density lipoprotein receptors. *Results:* Activity of low density lipoprotein receptors was defined as absent, being less than 2% of normal, in 4 patients who presented at the ages of 0.3, 1.4, 1.8, and 4.5 years, respectively. The activity was minimal, representing 5%–30% of normal, in another 4 patients presenting at the ages of 6.1, 9.6, 9.9, and 12 years, and was undetermined in 2 patients who presented at the ages of 3.5, and 12.1 years. Levels of low density lipoprotein cholesterol at presentation ranged from 12.2 to 24 millimoles per litre. Plasmapheresis was performed bi-weekly in 9 patients. Patients with absence of receptor activity were less likely to have a serial decrease in the levels of low density lipoprotein cholesterol prior to plasmapheresis, and one of these patients was increased to weekly plasmapheresis. In addition, they had more aggressive cardiovascular involvement of the coronary arteries, aortic valve and aorta, requiring surgical intervention at the age of 8 and 12 years in 2 patients, with sudden death at the age of 3.1 years in one patient. In contrast, 1 patient with minimal receptor activity had surgical intervention at the age of 16.6 years and another patient died suddenly at the age of 33.6 years. *Conclusion:* Complete cardiac assessment is recommended at presentation. The frequency of plasmapheresis should be adjusted according to the activity of low density lipoprotein receptors and the individual response of the patient.

Keywords: Plasmapheresis; homozygous familial hypercholesterolemia; therapy; outcome

Familial hypercholesterolemia is a common autosomally inherited co-dominant disease afflicting from between one in two hundred and one in five hundred individuals. It arises from a defect in the low density lipoprotein receptor gene.[1,2] This causes abnormalities or absence of the low density lipoprotein receptor, and impaired clearance of circulating low density lipoprotein,[1,3] resulting in high levels in the blood. More than 250 mutations of the gene have been characterized.[3] Defective alleles can be grouped as causing either an absence of receptor activity, defined as less than 2% of normal, in which either a non-functional or no receptor protein is produced, or minimal activity, from 5 to 30% of normal, in which an abnormal protein is produced with subnormal function. The type of functional defect affects the extent of elevation of the levels of low density lipoprotein cholesterol, and the risk and rate of development of atherosclerosis. Rarely, perhaps once in a million, a patient may be homozygous for familial hypercholesterolemia, with extreme

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elevations of low density lipoprotein cholesterol and aggressive development of atherosclerosis. The severity of the disease depends on the functionality of each of the two inherited abnormal alleles.

For homozygous patients, more extreme elevations of the lipoprotein require more extreme therapies, with little effect from conventional dietary and pharmacologic management.[4] Almost all patients require plasmapheresis or apheresis of low density lipoproteins,[5] although use of partial ileal bypass surgery,[6] liver transplantation,[7,8] and portocaval shunting[9] have been described. Gene therapy[10] remains an attractive future alternative. Many of these patients, nonetheless, develop evident atherosclerotic cardiovascular disease, often in the first and second decades of life. Over a period of 20 years, we have diagnosed and managed 10 patients with homozygous familial hypercholesterolemia. We sought to relate the magnitude of the functional abnormality in these rare patients, as assessed on the basis of activity of low density lipoprotein receptors, to their individual characteristics, their response to therapy, and the development of cardiovascular involvement.

Methods

The medical records of all patients assessed and managed at the Hospital for Sick Children, Toronto, Canada, were reviewed. Data were collected regarding individual characteristics, serial fasting lipid profile values, management, results of cardiologic testing, and interventions. Data are described as frequencies, medians with ranges, and means with standard deviations, as appropriate. Patients are grouped according to the activity of low density lipoprotein receptors. Absence of activity is considered to represent less than 2% of normal, while minimal activity accounts for 5%–30% of normal values. We have not yet characterized 2 patients. Given the small number of patients, differences between the groups are presented only with descriptive statistics.

Results

Population studied

The characteristics of the 10 patients, 8 of whom were male, are described in Table 1. The majority of patients presented for assessment of cutaneous lesions consistent with tuberous xanthomas. The diagnosis of homozygous familial hypercholesterolemia was confirmed in 8 patients by characterization of the mutation of the low density lipoprotein receptor, and assessment of its activity, from biopsied skin fibroblasts analyzed in the laboratory of Brown and Goldstein as previously published.[3] The diagnosis in the two remaining patients was made on the basis of clinical features, with evident heterozygous familial hypercholesterolemia in both parents. All patients, while fasting, had levels of low density lipoprotein cholesterol above 12 mmol/l at the time of presentation. The four patients with absent activity, ranging in age from 3 months to 3 years at presentation, were seen at younger ages, and with higher initial fasting levels of low density lipoprotein cholesterol, than those with minimal receptor activity. The four patients in this group presented between 6 and 12 years of age. No patient had symptoms or signs of cardiovascular disease at presentation.

Dietary and pharmacologic lipid-lowering therapy

All patients were placed on an American Heart Association Step 2 low fat, low cholesterol diet. Patients with absence of receptor activity had trials at various times of different lipid-lowering medications, such as cholestyramine, colestipol, niacin, or lovastatin, as did one of the patients with minimal receptor activity (Patient 3). These regimes had minimal effects on the levels of low density lipoprotein cholesterol. The mechanism of action of both the bile-acid binding resins and the hydroxymethylglutaryl coenzyme A reductase inhibitors, or "statins", is secondarily to upregulate the cellular production of low density lipoprotein receptors, which are deficient or defective in homozygous familial hypercholesterolemia. More recently in our patients, high doses of atorvastatin, a more potent "statin" drug, have been used as adjunctive therapy to produce more profound inhibition of synthesis of endogenous cholesterol, lowering more efficiently the levels of cholesterol.[11–14] Patients #1, 2, 3, 6, and 9 were treated with probucol, until it was no longer commercially available. Probucol is a potent antioxidant that also lowers the levels of low and high density lipoprotein cholesterol by about one-quarter in those with homozygous familial hypercholesterolemia by mechanisms independent of the low density lipoprotein receptor.[15] Oxidized low density lipoprotein cholesterol is known to be more atherogenic.

Plasmapheresis

Given the absent or inadequate response to diet and pharmacologic therapy, plasmapheresis and low density lipoprotein apheresis remain the cornerstone of therapy for patients with homozygous familial hypercholesterolemia. Plasmapheresis acutely lowers the levels of both low and high density lipoprotein cholesterol by about half.[16] The cardiovascular benefits of reduction in low density lipoprotein cholesterol do not seem to be negated by reductions in high density lipoprotein cholesterol.[17] Nonetheless, low density

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Table 1. Clinical summary of patients with homozygous familial hypercholesterolemia.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Male	Male	Male	Male	Male
Ethnic origin	Canadian	El salvador	Italian	French	German
LDL Receptor activity (%)	<2	<2	<2	<2	5
Mutation allele 1	Not characterized	Not characterized	FH Italy	FH French-Canadian 1	FH Cinc
allele 2	Not characterized	Not characterized	FH Italy	FH French-Canadian 1	Not characterized
Age at presentation (yrs)	1.4	3	0.3	1.8	12
Age at skin biopsy (yrs)	1.5	4.6	3.5	3.1	15.6
First lipid profile					
T chol (mmol/l)	20.1	25.44	23.79	24.57	15.34
LDL (mmol/l)	19.23	22.37	22.2	24	13.98
HDL (mmol/l)	0.52	0.75	0.57	0.72	0.83
TG (mmol/l)	0.76	2.9	2.24	5.08	1.16
Primary therapy	Plasmapheresis	Plasmapheresis	Plasmapheresis	Medications	Plasmapheresis
Current age (yrs)	13.6	13.3	21.2	Deceased (aged 3.1)	Deceased (aged 33.6)
Cardiac status	CABG (aged 8 yrs)	75% RCA ostial stenosis	Left main coronary ostioplasty (aged 12 yrs), right coronary ostioplasty and aortic valve repair (16.5 yrs); aortic valve replacement (aged 16.6 yrs)	Coronary artery occlusion	Coronary artery occlusion

Characteristic	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Gender	Male	Male	Male	Male	Male
Ethnic origin	Phillipino	Guyanan	Polish/French	Canadian	Canadian
LDL Receptor activity (%)	15–30	15–30	15–30	Not determined	Not determined
Mutation allele1	FH Phillip	Not characterized	FH French-Canadian	Not characterized	Not characterized
allele 2	Not characterized	Not characterized	FH Germany	Not characterized	Not characterized
Age at presentation (yrs)	9.6	9.9	6.1	8.0	2
Age at skin biopsy (yrs)	9.8	12.3	7.1	8.1	Not performed
First lipid profile					
T chol (mmol/l)	13.5	13.8	22.03	24.43	21.44
LDL (mmol/l)	12.17	12.66	22.01	23.12	20.35
HDL (mmol/l)	0.96	0.83	0.54	0.77	0.59
TG (mmol/l)	0.82	0.69	1.05	1.18	1.00
Primary therapy	Plasmapheresis	Plasmapheresis	Plasmapheresis	Plasmapheresis	Plasmapheresis
Current age (yrs)	21.7	32.0	20.8	12.1	3.5
Cardiac status	CABG (aged 16.6 yrs)	50% stenosis midportion of LAD & 60% stenosis of RCA	Moderate-severe aortic valve stenosis	Mild coronary artery stenosis	Stable

Abbreviations: LDL: low density lipoprotein; T chol: total cholesterol; HDL: high density lipoprotein; TG: triglyceride; CABG: coronary artery bypass graft; LAD: left anterior descending coronory artery.

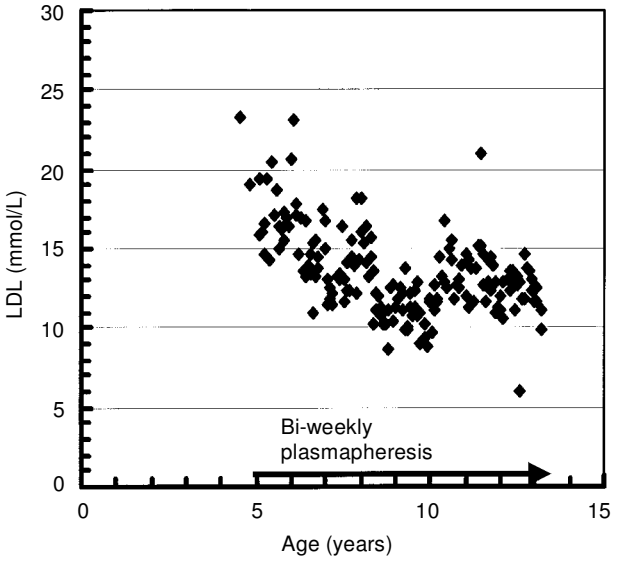

Figure 1.
Serial levels of low density lipoprotein cholesterol for patient #2. Plasmapheresis was performed bi-weekly from the age of 4.7 years, with significant reduction in levels of low density lipoprotein cholesterol prior to the next plasmapheresis, and a progressive downward trend. He is currently 13.3 years of age, and latest coronary angiography showed only a 75% stenosis of the origin of the right coronary artery, without any perfusion defect on stress nuclear medicine myocardial perfusion scanning. LDL, low density lipoprotein.

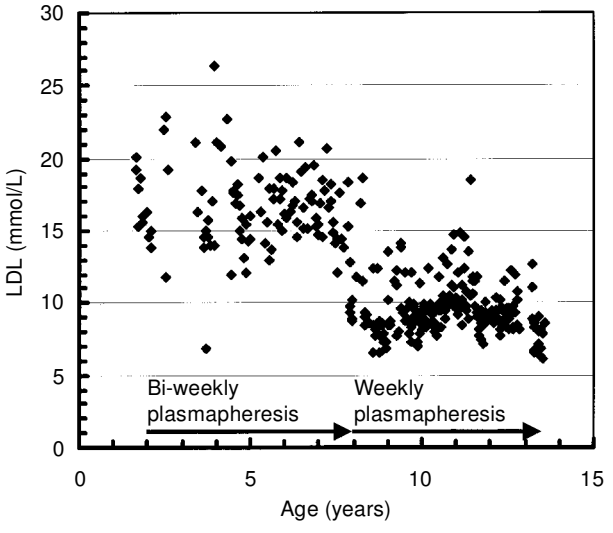

Figure 2.
Serial levels of low density lipoprotein cholesterol for patient #1. Plasmapheresis was performed bi-weekly from the age of 2 years, with frequent interruptions due to problems with central venous access. At the age of 8 years, he developed significant coronary arterial disease and underwent bypass grafting. Following this, plasmapheresis has been performed weekly, with better reduction in levels of low density lipoprotein cholesterol before the next plasmapheresis. LDL, low density lipoprotein.

lipoprotein apheresis, which selectively removes low density lipoprotein cholesterol, is preferred,[18–21] although it is not available at our center. The acute reductions of low density lipoprotein cholesterol with plasmapheresis are followed by a gradual return toward baseline within one to three weeks. Performing plasmapheresis repeatedly at uninterrupted intervals before the levels of cholesterol return to baseline results in a gradual progressive decline in the levels of low density lipoprotein cholesterol prior to plasmapheresis (Fig. 1). Initially, patients #1, 2, 3, 5, 7, 8, 9, and 10 were treated with bi-weekly plasmapheresis therapy. Patient #1 was started on bi-weekly plasmapheresis, but was advanced to weekly plasmapheresis after developing important coronary arterial disease at the age of 8 years (Fig. 2). Patient #4 died suddenly shortly after presentation before plasmapheresis could be considered. Patient #6 initially declined plasmapheresis, but later decided to start it at the age of 16.8 years after developing important coronary arterial disease. Patient #10 was started on plasmapheresis, but had recurrent problems with central venous access. Plasmapheresis was therefore withheld, and she has had comparable lipid-lowering with probucol and high dose atorvastatin. Overall, patients with absence of receptor activity had higher initial levels of low density lipoprotein cholesterol, with a more rapid return to baseline after plasmapheresis, resulting in overall less effective lowering of the low density lipoprotein cholesterol. In addition, all patients had regression of xanthomas while on plasmapheresis.

Complications of plasmapheresis in our patients have been rare, with only mild disturbances in the serum electrolytes and transient nausea. Complications related to the use of lines for central venous access, in contrast, have been important. Our tenth patient, who was very young, had an episode of sepsis related to an infection of the line, with secondary osteomyelitis. Another very young patient, #1, had multiple blockages and replacements of lines, with subsequent thrombotic occlusion of much of the venous system of the head and arms. The use of warfarin as prophylaxis, with no episodes of haemorrhagic complications or overdosing, has almost completely eliminated further episodes of occlusion of the lines by thrombus. A few of the families lived at some distance from our center, and made bi-weekly or weekly trips to our center. Patients who reached adult size or age were transferred to more local facilities for their plasmapheresis and medical follow-up, although we maintained close communication with the patients and families. All families adjusted rapidly to care of the line used for central

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venous access. Of note, patient #7 has had two successful pregnancies, during which she received her usual plasmapheresis, with no complications.

Cardiologic evaluation

Patients were assessed clinically every 6 months, undergoing 24-hour ambulatory electrocardiographic monitoring every 6 months until the age of 5 years, as well as standard 12 lead electrocardiograms and echocardiography yearly. When patients were old enough to exercise, stress nuclear medicine myocardial perfusion scans were performed yearly. More recently, dobutamine stress echocardiography has also been performed. Cardiac catheterization with coronary arteriography was performed at presentation, and routinely every 3 to 5 years thereafter, or if the patient developed cardiovascular symptoms or perfusion defects on a stress nuclear medicine myocardial perfusion scan. Cardiovascular disease in the patients is summarized in Table 1.

Coronary arterial disease

All patients except the youngest (patient #10) have had coronary arterial disease. All 4 patients with absence of receptor activity have developed disease earlier despite plasmapheresis, and this has occurred mainly at the level of the origins of the coronary arteries from the aorta. Three patients required intervention for coronary arterial disease, one of whom also required repair, then replacement, of the aortic valve. Two of these patients had absence of receptor activity (patients #1 and 6), with the third having minimal activity (patient #6) but refusing plasmapheresis until becoming symptomatic from coronary arterial disease. In addition, two patients died from coronary arterial disease without previous cardiac intervention. One of these patients, who had absence of receptor activity (patient #4) died at the age of 3.1 years shortly after presentation, and had occlusion of both coronary arteries, while the other patient with 5% receptor activity (patient #5), and receiving plasmapheresis but refusing any cardiologic evaluation, died suddenly at the age of 33.6 years. Occlusion of the orifice of the main stem of the left coronary artery was noted at autopsy. Of these 5 patients requiring intervention, or who died, only patient #3, with atypical chest pain, and patient #6 with syncope on exercise, had symptoms.

Aortic valvar and aortic disease

All patients are monitored serially with echocardiography, and more recently with magnetic resonance imaging, for aortic valvar and aortic involvement. Two patients have developed important atherosclerotic aortic valvar disease. One patient with absence of receptor activity (patient #3) developed both supravalvar and valvar aortic stenosis. Following an initial aortic valvotomy, and patching of the aortic root, there was progressive aortic regurgitation. The valve was repaired, but symptoms and regurgitation persisted. At the age of 16.6 years, the aortic valve was replaced with a 21 mm Carbomedics valve using a Konno procedure. The second patient with 15%–35% receptor activity (patient #8) has developed moderate to severe aortic valvar stenosis with chest pain, and will undergo aortic valvotomy. In addition, extensive atherosclerosis of the aortic root was noted at autopsy in patient #5, and patient #6 has mild aortic valvar thickening.

Patient #1 had mild thickening of the ascending and descending thoracic aorta with moderate disease of the abdominal aorta. Patient #2 has aortic root calcification and mildly thickened aortic and mitral valves, with mild stenosis of the left common carotid artery. Patient #6 has mild thickening of the ascending aorta with mild stenosis of the right common carotid artery. Patient #7 has mild aortic root thickening. Patient #8 has extensive thickening of the ascending aorta and aortic isthmus, with stenosis of the origin of the left subclavian artery. Patients #9 and #10 currently show no evidence of aortic or other vascular disease.

Discussion

Homozygous familial hypercholesterolemia

Patients who are homozygous for familial hypercholesterolemia inherit two abnormal genes for low density lipoprotein receptors, and consequently have no or minimally functioning receptors. Their concentrations of low density lipoprotein cholesterol in the plasma range from 12 to 25 mmol/l, resulting in greatly accelerated atherosclerosis, and well as xanthomatous deposition of cholesterol in the skin and tendons with associated corneal arcus. Patients typically present in infancy and early childhood as a result of cutaneous lesions. On a cellular level, accumulations of lipid can be found in vascular tissue, and in skin, tendons, and various other extravascular sites. Commonly described cardiovascular lesions include atherosclerosis of the ascending and descending aorta, coronary ostial lesions, coronary arterial disease, and disease of the aortic and mitral valves.[22] Foam cell transformation of macrophages occurs in the media of arterial walls, leading to formation of atherosclerotic plaques. The atherosclerotic lesions tend to be dominated by their greatly increased lipid content, and are softer and more friable. Foam cells with fibrous thickening are often seen in the aortic and mitral valvar tissues. If untreated, patients have manifestations of coronary arterial disease by the

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age of 10 years.[23] We have previously reported that death from myocardial infarction can occur as early as 3 years of age.[24]

As homozygous familial hypercholesterolemia is very rare, previous reports are limited to small series of patients, often derived from a single pedigree. Our population is distinct in the number and diverse origins of the patients, with all being treated and monitored with a similar regime. The variable nature of homozygous familial hypercholesterolemia makes comparative assessment of patients more difficult. Characterization of the mutation and level of receptor activity appears to have important implications for therapy and prognosis, as noted in our population.

Cardiovascular complications

The cardiovascular state of these patients is variable, and important cardiovascular disease may be manifest at diagnosis. The symptoms of cardiovascular disease in children are more often atypical, as evident in our patients who were either asymptomatic, or had symptoms of atypical chest pain or syncope. Complete baseline assessment at diagnosis, and careful routine monitoring, is mandatory.

Cardiovascular involvement is more aggressive and slightly different than typical atherosclerosis. Involvement of the aorta, and the aortic and mitral valves, is important. Coronary arterial lesions are often at the origins of the arteries from the aorta, and may reflect involvement of the aortic root. It has been shown that orificial stenosis is the most common anatomical correlate with anginal symptoms in this group of patients.[22] Activity of low density lipoprotein receptors, and its affect on levels of low density lipoprotein cholesterol in the plasma, is a strong predictor of the aggressiveness of cardiovascular involvement, and also relates to the age at presentation and response to therapy. In a review of 13 patients, Sprecher et al.[25] found the onset of angina to occur earliest in those patients with the lowest receptor activity. Three patients died during their study, all under the age of 15 years, and all had receptor activity of 3% or less.

Management of hypercholesterolemia

Hypercholesterolemia in patients with heterozygous familial hypercholesterolemia is often resistant to single drug therapy, and treatment target levels are often not achieved, even after combination therapy with 2 or 3 drugs.[26] For patients who are homozygous, drug therapy is even less effective, since the effects of the majority of cholesterol-lowering medications are mediated by upregulation of low density lipoprotein receptors, which are often not present or poorly functional in homozygous patients. Probucol has been used in homozygous patients, and in addition to potent antioxidant properties, has been shown to reduce levels of low density lipoprotein cholesterol by about one-quarter, with important regression of xanthomas.[15] But it also significantly lowers the levels of high density lipoprotein cholesterol. Various other therapies for homozygous patients have been described, and been generally proven to be only partially effective at best. Surgical procedures, such as porta-caval bypass, have been shown to cause only transient reductions in levels of cholesterol, and are associated with gastrointestinal upset, loss of weight, and encephalopathy.[6]

There is increasing evidence that long-term plasmapheresis, particularly apheresis specific for low density lipoprotein, can be effective in lowering levels of low density lipoprotein and preventing or slowing the progression of atherosclerotic vascular disease, especially in the coronary arteries.[21] Thompson et al.[17] have shown that bi-weekly apheresis is effective in significantly reducing total levels of cholesterol and its low density lipoprotein component (Table 2). In our study, bi-weekly plasmapheresis, that was not specific for low density lipoprotein resulted in a reduction in low density lipoprotein cholesterol of about one-half. More frequent plasmapheresis may be required to maintain reduction in

Table 2. Literature review of plasma exchange/plasmapheresis in homozygous familial hypercholesterolemia

Study	Year	Number	Plasma exchange of cases	% reduction in schedule LDL levels
King ME et al.[16]	1980	2	Bi-weekly	30–39
Thompson GR et al.[17]	1985	5	Bi-weekly	37
Berger GM et al.[19]	1990	2	Weekly Bi-weekly	50–80
Thiery J et al.[18]	1990	1	Weekly	66
Zwiener et al.[20]	1995	2	Weekly Bi-weekly	63–68

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levels for patients with an absence of receptor activity. Plasmapheresis is a safe method to reduce low density lipoprotein cholesterol, and the only complications encountered were those related to vascular access, which we have reduced with the adjunctive use of low dose anticoagulation therapy. Other problems that may occur include abdominal cramps, transient urticaria, and abnormal vaso-vagal response.[20] Other more aggressive regimens of plasmapheresis have been reported, including twice weekly regimens, without a significant increase in associated complications.[19] Thompson et al.[17] showed that the reduction by half in levels of low density lipoprotein cholesterol attributable to plasmapheresis significantly improved life expectancy of 5 patients compared to their untreated homozygous familial hypercholesterolemia siblings, those treated surviving an average of 5 years longer.

While drug therapy is insufficient, recent evidence suggests that the hydroxymethylglutaryl coenzyme A reductase inhibitors may have an adjuvant role in causing further reductions in levels of low density lipoprotein cholesterol when combined with plasmapheresis. Thiery et al.[18] described an additional reduction of one-fifth from levels prior to plasmapheresis when low-dose lovastatin was added to a weekly regime of plasmapheresis. Recent studies with the more potent atorvastatin have shown additional lowering when used in higher doses, particularly for patients who have some minimal receptor activity.[11–14] Experience in our patients has likewise been encouraging, particularly in our most recent patient, in whom the combination of atorvastatin 40 mg per day and probucol has lowered the levels in the plasma from 21 to less than 10 mmol/l.

Other techniques of plasmapheresis have been reported, including the use of dextran sulphate cellulose columns having a specific affinity for low density lipoprotein cholesterol. Current non-specific plasmapheresis removes high density lipoprotein as well as low density lipoprotein cholesterol, whereas levels of high density lipoprotein cholesterol are more preserved with columns specific for low density lipoprotein. A major disadvantage of plasmapheresis, particularly the form specific for low density lipoprotein, is its great expense.[20]

Important psychosocial issues must also be addressed as part of the management of these rare patients. Ose[27] outlined the psychosocial barriers impeding the effective diagnosis and treatment of familial hypercholesterolemia, including the effects of being labeled or identified as a person with a disease, the difficulty in obtaining adequate insurance and employment, the ethics of contacting relatives, and the importance of counseling regarding reproduction and inheritance.

Conclusion

Homozygous familial hypercholesterolemia is a rare, dominantly inherited metabolic disorder resulting in extremely elevated levels of low density lipoprotein cholesterol and aggressive atherosclerotic involvement of the cardiovascular system. All of these patients require complete cardiovascular investigation at the time of presentation, as important coronary arterial atherosclerosis can be present at very young ages. Careful monitoring is necessary to detect asymptomatic disease. The type of mutation, and the level of low density lipoprotein receptor activity, are important factors to guide therapy and prognosis. Aggressive lipid-lowering therapies are necessary, including plasmapheresis and adjunctive therapy with high dose hydroxymethylglutaryl coenzyme A reductase inhibitors. Pediatric cardiologists are integral members of the multidisciplinary team required for management of these patients.

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