Atherosclerosis, 61 (1986) 1–6
Elsevier Scientific Publishers Ireland, Ltd.

ATH 03785

Causes of Death in Patients with Familial Hypercholesterolemia

H. Mabuchi [1], S. Miyamoto [2], K. Ueda [3], M. Oota [4], T. Takegoshi [5], T. Wakasugi [1] and R. Takeda [1]

[1] *Second Department of Internal Medicine, Kanazawa University School of Medicine, Kanazawa;*
[2] *Department of Internal Medicine, Hokuriku Hospital, Kanazawa;*
[3] *Department of Internal Medicine, Komatsu Municipal Hospital, Komatsu;*
[4] *Department of Internal Medicine, Takaoka Municipal Hospital, Takaoka; and*
[5] *Department of Internal Medicine, Fukui Prefectural Hospital, Fukui (Japan)*

(Received 14 January, 1986)
(Accepted 3 February, 1986)

Summary

Five out of 15 homozygotes and 41 out of 527 heterozygotes of familial hypercholesterolemia (FH) died during the past 10 years. Sudden death or heart failure was the cause of death in each of the 5 deceased homozygotes. Twenty heterozygotes died of myocardial infarction, 9 of sudden death, and 1 died after AC bypass surgery. Thus, 30 heterozygotes (73.2%) died of coronary heart disease (CHD). The mean age of death was significantly younger in male heterozygotes (54 years) than in the females (68 years).

Rate of death from CHD in heterozygotes was 11 times higher than in the general population in Japan. Rate of death from pancreas cancer in FH was significantly higher than in the general population. These results suggest that FH is highly associated with pancreas cancer as well as CHD.

Key words: *Causes of death – Coronary heart disease – Familial hypercholesterolemia*

This work was supported by a Scientific Research Grant of the Education Ministry of Japan (No. 59480198) and grants for Primary Hyperlipidemia Research Projects of the Welfare Ministry of Japan.

Address reprint requests to Hiroshi Mabuchi, M.D., Second Department of Internal Medicine, Kanazawa University School of Medicine, Takara-machi 13-1, Kanazawa, Ishikawa 920, Japan.

Abbreviations: AC = bypass, aortocoronary bypass; CHD = coronary heart disease; FH = familial hypercholesterolemia; LDL = low-density lipoprotein; SCPK = serum creatinine phosphokinase; SGOT = serum glutamic oxaloacetic transaminase; SLDH = serum lactate dehydrogenase.

Introduction

Familial hypercholesterolemia (FH) is one of the most common inherited disorders in Japan [1] as well as in Western countries [2], occurring in approximately one out of 500 people. FH is characterized by a defect in low density lipoprotein (LDL) metabolism and is frequently associated with premature coronary heart disease (CHD) [2]. We have studied the causes of death in FH patients, and have compared the findings with the

general population of Japan where CHD is still uncommon as a cause of death. We suggest that in addition to CHD, hypercholesterolemia is also associated with cancer of the pancreas.

Patients and Methods

FH was diagnosed according to the following two criteria: (1) primary hypercholesterolemic patients (arbitrarily above 230 mg/dl in any age group) with tendon xanthomas, and (2) primary hypercholesterolemic patients with and without tendon xanthomas in a first-degree relative of familial hypercholesterolemic patients. The diagnosis of homozygous FH was made in hypercholesterolemic patients with generalized xanthomas whose parents had been proven to have heterozygous FH.

The diagnosis of myocardial infarction was accepted when the following 3 criteria were fulfilled: (1) characteristic clinical history, (2) serial changes in ECG suggesting or proving myocardial infarction (Q-waves) or injury (ST elevations), and (3) transient increase of SGOT, SCPK or SLDH.

The causes of death were based on autopsy studies, hospital records or interviews with the attending doctors. Sudden death was recorded if death occurred within 15 min of the onset of symptoms with no specific cause. Malignancy cases were confirmed by surgical operation or autopsy.

Serum cholesterol and triglyceride levels were determined by enzymatic methods.

The χ^2-test was a statistical procedure used for comparing FH with the general population. The unpaired t-test was used to compare male and female FH patients.

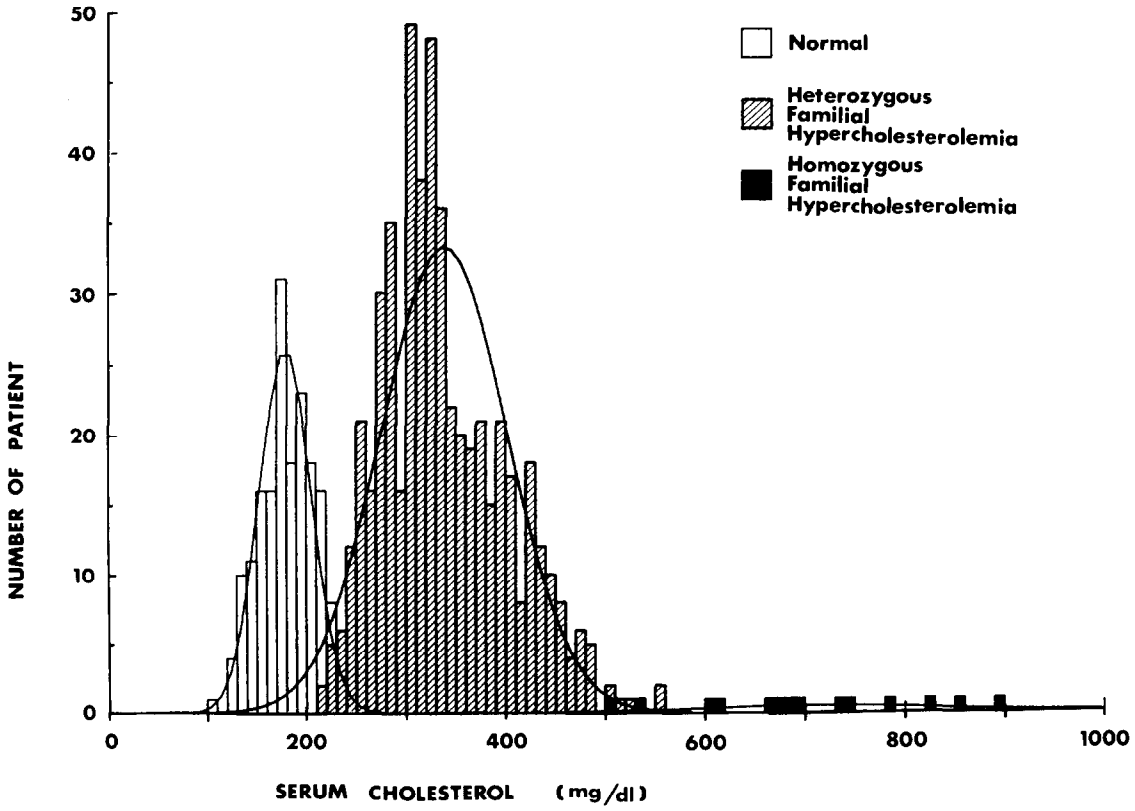

Fig. 1. Distributions of serum cholesterol levels in normal subjects, and in heterozygous and homozygous patients with familial hypercholesterolemia.

TABLE 1

DETAILS OF PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

No.	Patient	Age (yr)	Sex (F/M)	Serum cholesterol (mg/dl)	Serum triglyceride (mg/dl)	Cause of death [a]	Autopsy
1	Y.E.	16	M	900	300	Heart failure	No
2	M.I.	22	F	730	237	SD	No
3	K.Y.	31	F	609	126	SD	No
4	K.M.	42	F	610	180	SD	No
5	S.T.	18	M	781	189	Heart failure	Yes
Mean		26		726	206		
SD		11		123	66		

[a] SD = Sudden death.

TABLE 2

DETAILS OF MALE PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

No.	Patient	Age (yr)	Serum cholesterol (mg/dl)	Serum triglyceride (mg/dl)	ECG findings [a]	Achilles tendon thickness [b] (mm)	Cause of death [c]	Autopsy
1	I.O.	43	378	153	+ +	16	MI	Yes
2	Y.O.	33	307	82	−	10	Accident	No
3	T.K.	51	395	163	+ +	10	MI	No
4	Y.O.	63	355	57	+	17	SD	No
5	T.K.	64	346	134	+ +	22	Ca of kidney	Yes
6	H.Y.	43	335		+ +		SD	No
7	Y.K.	36	300				SD	No
8	S.N.	59	324	122	+ +	16	MI	Yes
9	T.N.	47	500		+ +		SD	No
10	K.E.	42	350	78	+ +		SD	No
11	M.M.	57	468	212	+ +		Stroke	No
12	R.I.	59	295	260	+ +	9	MI	No
13	K.W.	54	308	303	+	14	Ca of pancreas	No
14	K.M.	48	400	118	+	13	Ca of esophagus	No
15	H.T.	47	378	192	+ +	9	MI	No
16	K.O.	58	376	146	+		AC-bypass surgery	No
17	W.M.	73	308	133	+ +	15	MI	No
18	S.T.	32	483	85	+ +	15	MI	No
19	S.M.	69	415	115	+ +		MI	Yes
20	S.T.	75	302	112		10	Ca of pancreas	Yes
21	S.M.	49	306	230	+		Ca of pancreas	No
22	S.M.	65	450		+ +		MI	No
23	K.I.	44	423		+ +		SD	No
24	A.N.	63	281	356	+ +	9	MI	No
25	T.S.	72	280		+ +	15	MI	Yes
Mean		54	363	161		13		
SD		12	65	80		4		

[a] ECG findings: − = Normal, + = Angina pectoris with more than 1 mm flat ST-segment depression, + + = Myocardial infarction with abnormal Q-wave.

[b] Normal value in Japanese subjects; 6.3 ± 0.2 mm (mean ± SEM).

[c] MI = myocardial infarction; SD = sudden death; Ca = cancer.

TABLE 3

DETAILS OF FEMALE PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

No.	Patient	Age (yr)	Serum cholesterol (mg/dl)	Serum triglyceride (mg/dl)	ECG findings [a]	Achilles tendon thickness [b] (mm)	Cause of death	Autopsy
1	C.H.	62	323	64	+ +	16	MI	Yes
2	T.S.	69	326	113	+ +	18	MI	Yes
3	A.N.	61	362	162	+	18	Ca of gallbladder	No
4	T.S.	63	557	107	+ +	14	Stroke	Yes
5	M.S.	64	398	84	+ +		MI	Yes
6	M.U.	73	332	104	+ +	15	MI	No
7	M.N.	61	353	227	+ +		MI	Yes
8	Y.M.	71	373	78	+ +	12	MI	Yes
9	F.K.	54	279	97	+ +	18	SD	No
10	S.A.	72	390	143	+ +	22	SD	No
11	R.K.	77	318	250	+		SD	No
12	M.K.	63	349	193	+ +	11	MI	No
13	N.T.	73	312	112			Stroke	No
14	K.T.	85	343	211	+ +		MI	Yes
15	S.N.	74	256	148	+ +		MI	No
16	S.S.	70	319	95	+		Stroke	No
Mean		68	349	137		16		
SD		8	67	57		4		

[a,b,c] See Table 2.

Results

During the past 10 years, 15 homozygotes and 527 heterozygotes of FH were examined in Kanazawa University Hospital and its affiliated hospitals. Their serum cholesterol levels, including those of unaffected family members, are shown in Fig. 1. Their trimodal distributions of serum cholesterol levels are evident. Mean serum cholesterol levels (±SD) of unaffected subjects (n = 173), heterozygotes of FH (n = 527) and homozygotes of FH (n = 15) were 179 ± 26, 338 ±

TABLE 4

CAUSES OF DEATH, SEX, AGE, SERUM CHOLESTEROL AND TRIGLYCERIDE LEVELS IN 41 PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Values are given as means ± SD.

Cause of death	No. of case		Age (yr)		Serum cholesterol (mg/dl)		Serum triglyceride (mg/dl)	
	M	F	M	F	M	F	M	F
Myocardial infarction	11	9	58 ± 13	69 ± 8	362 ± 70	339 ± 39	175 ± 85	136 ± 61
Sudden death	6	3	46 ± 9	68 ± 12	377 ± 72	329 ± 56	68 ± 15	163 ± 79
Death after AC bypass	1	0	58	–	376	–	146	–
Stroke	1	3	57	69 ± 5	468	396 ± 140	212	105 ± 9
Cancer	5	1	58 ± 11	61	332 ± 42	362	179 ± 84	162
Accident	1	0	33	–	307	–	82	–
Mean ± SD	25	16	54 ± 12	68 ± 8	363 ± 65	349 ± 67	161 ± 80	137 ± 57

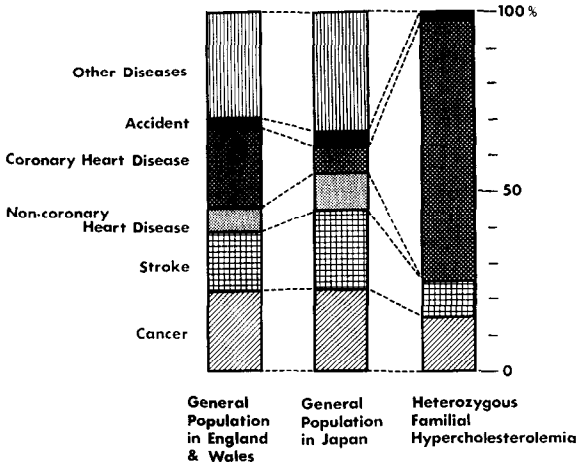

Fig. 2. Causes of death in heterozygous patients with familial hypercholesterolemia, and in the general populations of Japan, and England and Wales.

63 and 713 ± 122 mg/dl, respectively.

Sudden death or heart failure was the cause of death in each of the 5 deceased homozygotes of FH (Table 1). Case Y.E. died of heart failure due to acquired stenosis of the aortic root. Case S.T. died of heart failure due to supravalvular stenosis and ischemic cardiomyopathy. Their average age at death was 26 years, with an average serum cholesterol level of 726 mg/dl.

Forty-one of the 527 heterozygotes of FH died during the past 10 years (Tables 2 and 3). Autopsies were performed in 13 cases (32%). Twenty patients died of myocardial infarction, 9 of sudden death, and 1 patient died after AC bypass surgery. Thus, 30 patients (73.2%) died of CHD. Four heterozygotes (10%) died of strokes. Out of 6 patients who died of cancer, 3 died of cancer of the pancreas. The mean age at death was significantly younger in male heterozygotes (54 years) than in female heterozygotes (68 years) ($P < 0.001$) (Table 4).

Rates of death from CHD in heterozygotes of FH (73.2%) was 10.9 and 2.8 times higher than in the general population of Japan (6.7%, $P < 0.005$) [3], and in England and Wales (26.6% [4], $P < 0.005$), respectively. The percentage of deaths from strokes and cancer in FH was not significantly different from that in the general population (Fig. 2). However, death from pancreatic cancer (7.5%) in FH was significantly higher than in the general population (1.2%) in Japan [3,4].

Discussion

It is commonly accepted that FH is highly associated with CHD [2]. In homozygous FH, coronary arterial stenosis and aortic supravalvular stenosis caused by atherosclerotic changes were demonstrated through angiographies and autopsies [5–7]. The life expectancy of homozygous patients with FH is known to be limited to their second or third decades, the cause of death always being atherosclerotic cardiovascular diseases [1,2,7], as our present study indicates.

As for heterozygotes, the onset of CHD is reported to occur 10 years earlier in men than in women [8]. In the present study, the mean age at death from CHD in 18 male heterozygotes (mean ± SD; 54 ± 13) was significantly lower than that in female heterozygotes (69 ± 8). The present study made no attempt to lower serum lipid concentrations and there were no significant differences in serum cholesterol and triglyceride levels in male and female patients. Therefore, some other risk factors might have produced the difference in ages of death in males and females, as is true of the general population.

Heiberg showed that there were more cardiovascular deaths in 172 males and 164 females with xanthomatosis than in the general population [10]. The groups with myocardial infarction and sudden death combined accounted for 75 and 80% of the deaths in males and females, respectively. In the present study, the incidence of cardiovascular deaths in FH was 10.9 times higher than the general population of Japan. [3]. Although myocardial infarction of FH is more frequent and appears earlier than in the general population, the greatest difference is found in the proportion of sudden deaths. Jensen et al. [11] reported that 32(51.6%) out of 62 deceased members died of manifest coronary disease and 10(16.1%) died suddenly. In the present study 20(48.8%) out of 41 died of myocardial infarction and 9(22.0%) died suddenly. Death from cerebrovascular disease is reported to be less frequent in xanthomatosis patients than in the general population [10]. In the present study no difference was observed in death from cerebrovascular disease in patients with FH and in the general population of Japan.

A number of reports have been published indi-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.