

Screening for Familial Combined Hyperlipidemia in Children Using Lipid Phenotypes

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The purpose of this study was to screen for FCHL in children using serum lipid phenotypes. The subjects were 1,190 (599 male, 591 female) children who participated in a screening and care program for life style-related diseases in school children. Total cholesterol, high-density lipoprotein cholesterol and triglyceride were determined, and information on the family history of parents was obtained by questionnaire. Candidates for FCHL were screened by the following criteria; type IIb hyperlipidemia, type IIa hyperlipidemia with positive family history of CHD, hyperlipidemia or both. We informed them of the results by mail. A second series of examinations to diagnose FCHL was performed on volunteer participants, including their parents. The candidates consisted of 9 children with type IIb and 27 with type IIa hyperlipidemia, 11 of whom participated, in the second series of examinations, in which 5 children were diagnosed with FCHL. The prevalence was 0.4%, suggesting that at least half of all individuals with FCHL already demonstrate hyperlipidemia in childhood. *J. Atheroscler Thromb, 2003; 10: 299–303.*

Key words: Familial combined hyperlipidemia (FCHL), Serum lipid phenotype, Screening

Introduction

Familial combined hyperlipidemia (FCHL) is a common dominantly-inherited disorder with a prevalence of 1.0% in Japan (1). In 1973, FCHL was first reported as the leading cause of premature coronary heart disease (CHD) (2). However, its genetic background remains uncertain. In order to achieve primary prevention of CHD, carriers should be identified by screening before the development of atherosclerosis. It is well known that even in childhood, many affected individuals already demonstrate the characteristic serum lipid profile, with elevations in total cholesterol (TC), triglyceride (TG), or both (3–7). Also, most children with type IIb hyperlipidemia have FCHL (7).

The purpose of this study was to screen for FCHL using serum lipid phenotypes in children.

Subjects and Methods

The subjects were 1,190 (599 male, 591 female) children who participated in a screening and care program for life style-related diseases in school children in 2000. Five hundred and eighty children were fourth-grade students in elementary schools (9–10 years old), and 610 were first-grade students in junior high schools (12–13 years old). Standing height and body weight were measured, and TC, high-density lipoprotein cholesterol (HDL-C) and TG were determined after overnight fasting. TC and TG levels were measured by enzymatic methods. HDL-C was determined by a direct enzymatic method. Low-density lipoprotein cholesterol (LDL-C) was calculated by means of the Friedewald equation. Information on the family history was obtained from the parents using a questionnaire, which was completed at home by the students and their family members. The questionnaire included data about history of CHD, hyperlipidemia and diabetes mellitus.

According to the screening and care program for life style-related diseases in school children in Japan, the cut-off

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points of hypercholesterolemia, hypertriglyceridemia and low HDLC level were 200 mg/dl, 150 mg/dl and 40 mg/dl, respectively (8, 9). Children were classified using these cut-off points for hypercholesterolemia (IIa), hypertriglyceridemia (IV), and combined hyperlipidemia (IIb).

Candidates for further examinations to diagnose FCHL were screened by the following criteria;

1. Type IIb hyperlipidemia (TC = or > 200 mg/dl and TG = or > 150 mg/dl).

2. Type IIa hyperlipidemia (TC = or > 200 mg/dl) and positive family history of CHD, hyperlipidemia or both.

We sent the results to the candidates by mail, and recommended further examinations for them as well as their family members to determine the etiology in each candidate.

In the second series of examinations, we investigated serum lipids and insulin in volunteer participants. The diagnosis of FCHL was made according to the criteria reported by the Primary Hyperlipidemia Research Group formed by the Japanese Ministry of Health, Labor and Welfare (8). In adults, the cut-off points of hypercholesterolemia and hypertriglyceridemia were 220 mg/dl, and 150 mg/dl, respectively. The criteria comprise both major and minor items as follows:

Major items:

1. Proband reveals phenotypic expression of IIa, IIb or IV.

2. Affected first-degree relatives show one of the above phenotypes, and at least one of them (including the proband) shows IIa or IIb.

3. Familial hypercholesterolemia should be excluded according to the diagnostic criteria of FH (8).

Minor items:

1. Serum total cholesterol level less than 300 mg/dl in

most affected families and the proband.

2. Observed phenotypic change (e.g., from IIa to IIb).

3. Worsening of hyperlipidemia at postpubertal age.

4. Not associated with Achilles tendon xanthomatosis.

We obtained written informed consent from each child and family member.

Statistical Analysis

The differences in mean values were analyzed by a non-parametric method (Mann-Whitney U test). A *p* value less than 0.05 was considered to indicate statistical significance.

Results

Prevalence of serum lipid phenotypes

Type IIa, IIb and IV were found in 18.7%, 0.76% and 1.6%, respectively.

Characteristics of candidates for FCHL (Table 1)

The candidates consisted of 9 children with type IIb and 27 with type IIa who had a positive family history of hyperlipidemia, CHD or both. Hypo-HDL cholesterolemia (< 40 mg/dl) was found in one child with type IIb, and hypertension (> 135/80 mmHg) was also found in one with type IIb. Obesity (= or > 120% of standard weight for age, sex and height (10)) was identified in 5 (18.5%) of the 27 with type IIa and 8 (88.8%) of the 9 with type IIb.

Characteristics of non-participants (Table 2)

The mean values (standard error) of serum lipids for non-participants were 228.1 (9.4) mg/dl for TC, 99.6 (9.9) mg/dl for TG, 141.3 (9.7) mg/dl for LDLC and 66.9 (2.8) mg/dl

Table 1. Characteristics of candidates.

	Candidates <i>n</i> = 36	Non-candidates <i>n</i> = 1154	<i>p</i> value
Age (yr)	11.3 ± 0.3	11.1 ± 0.1	0.6748
Sex (male : female)	14 : 22	586 : 568	
Height (cm)	145.4 ± 1.6	145.6 ± 0.3	0.9747
Weight (kg)	41.7 ± 1.6	39.0 ± 0.3	0.084
Obesity index	10.6 ± 2.9	3.0 ± 0.5	0.0063
Systolic blood pressure (mmHg)	118.6 ± 1.8	113.4 ± 0.4	0.0124
Diastolic blood pressure (mmHg)	62.5 ± 1.2	61.1 ± 0.2	0.2385
Total cholesterol (mg/dl)	226.8 ± 6.9	175.6 ± 0.8	< 0.0001
HDL-cholesterol (mg/dl)	65.4 ± 6.9	63.5 ± 0.4	0.4644
LDL-cholesterol (mg/dl)	142.1 ± 7.1	99.4 ± 0.7	< 0.0001
Triglyceride (mg/dl)	96.8 ± 8.1	63.3 ± 0.9	< 0.0001

Mean ± SE

dl for HDLC. These were not significantly different from the values for the participants: 223.7 (8.5) mg/dl, 90.5 (14.8) mg/dl, 143.7 (8.2) mg/dl, 61.9 (4.2) mg/dl, respectively.

Characteristics of participants (Table 3)

Eleven children (9 with type IIa, 2 with type IIb) volunteered to participate in the second series of examinations. How-

ever, no parent of the 6 candidates participated. Among 7 participating first-degree relatives (2 fathers and 5 mothers) in 5 families, 3 cases of type IIa, 2 of type IIb and 2 of normolipidemia were found. The father of Case 3 had a history of CHD, but it was not possible to investigate his serum lipids. According to the diagnostic criteria of FCHL, 5 candidates, all who participated with at least one parent, were diagnosed as having FCHL.

Table 2. Characteristics of non-participants.

	Participants <i>n</i> = 11	Non-participants <i>n</i> = 25	<i>p</i> value
Age (yr)	10.6 ± 0.5	11.5 ± 0.3	0.1223
Sex (male : female)	4 : 7	10 : 15	
Height (cm)	144.9 ± 3.3	145.6 ± 9.0	0.9726
Weight (kg)	43.8 ± 3.6	40.8 ± 1.6	0.4922
Obesity index	16.7 ± 5.2	7.9 ± 3.4	0.1444
Systolic blood pressure (mmHg)	119.7 ± 2.3	118.1 ± 2.4	0.8368
Diastolic blood pressure (mmHg)	63.1 ± 1.6	62.2 ± 1.5	0.8100
Total cholesterol (mg/dl)	223.7 ± 8.5	228.1 ± 9.4	0.8907
HDL-cholesterol (mg/dl)	61.9 ± 4.2	66.9 ± 2.8	0.3719
LDL-cholesterol (mg/dl)	143.7 ± 8.2	141.3 ± 9.7	0.3363
Triglyceride (mg/dl)	90.5 ± 14.8	99.6 ± 9.9	0.6929

Mean ± SE

Table 3. Characteristics of participants.

Case	Sex	Age (year)	Obesity Index	TC (mg/dl)	HDLC (mg/dl)	TG (mg/dl)	LDLC (mg/dl)	Insulin (IU/ml)	Phenotype	Family History CHD
1	F	13	36.0	201	35	191	127.8	26	IIb	/
2	M	12	- 18.3	200	84	95	97.0	6	IIa	/
3	F	12	- 0.8	242	52	111	167.8	14	IIa	Father
	Mother	/	BMI = 20.4	242	53	168	155.4	11	IIb	
4	F	13	19.3	284	75	82	192.6	24	IIa	/
	Mother	37	BMI = 26.7	225	80	57	133.6	4	IIa	
5	F	9	31.4	200	59	37	133.6	9	IIa	Maternal grandfather
	Father	40	BMI = 26.5	229	45	152	153.6	12	IIb	
	Mother	33	BMI = 19.6	192	82	99	90.2	3	N	
6	F	10	33.0	206	54	169	118.2	12	IIb	/
7	M	12	25.9	231	69	51	151.8	14	IIa	/
8	F	9	19.2	261	72	65	176.0	14	IIa	/
	Mother	36	/	257	81	57	164.6	7	IIa	
9	F	9	6.3	223	73	75	135.0	6	IIa	/
10	M	9	2.9	206	51	55	144.0	8	IIa	/
11	M	9	29.3	207	57	65	137.0	8	IIa	/
	Father	54	BMI = 27.5	195	56	144	110.2	9	N	
	Mother	51	BMI = 19.2	272	91	66	167.8	5	IIa	

Obesity Index: ((body weight - standard weight) / standard weight) × 100

TC: total cholesterol, HDLC: high density lipoprotein cholesterol, TG: triglyceride, LDLC: low density lipoprotein cholesterol

IIa, IIb: phenotype of Fredrickson/WHO classification of hyperlipidemia, N: normolipidemia

Discussion

In this study, we diagnosed 5 children with FCHL out of 1190 children, with a prevalence of 0.4%. This is lower than that in the Japanese adult population (1), but suggests that at least half of all individuals with FCHL already demonstrate hyperlipidemia in childhood. The general characteristic serum lipid profile in FCHL usually becomes manifest in the postpubertal period, influenced by age and weight gain (3, 6, 10). Therefore, the prevalence of FCHL in children differs among the literature (2, 4, 8).

Our criteria for selecting candidates consisted of serum lipid phenotype and family history. The type IIb phenotype is supposed to show some familial features. Polonsky *et al.* (12) reported that the parents of children with two lipid abnormalities (high LDLC, together with high TG or low HDLC) tended to be obese, and that type IIb in a parent was a good predictor of hyperlipidemia in the child (13). Young Japanese children with type IIb were mostly diagnosed as FCHL (7). In this study we found 9 children with type IIb, with a prevalence of 0.76%. Type IIb hyperlipidemia was very rare in children, but some of them had other risk factors such as hypertension, hyperinsulinemia and low HDLC level, and all except one were obese. It is well known that FCHL is often associated with hyperinsulinemia, impaired glucose tolerance and obesity. However, there were not sufficient children with type IIb to screen for FCHL during childhood, because all children diagnosed with FCHL had type IIa in this study. In the second series of examinations, type IIb was found in one case (Case 4). The phenotype in FCHL may change during the course of the disease. Furthermore, especially in children, even carriers of FCHL may not yet manifest hypertriglyceridemia, because TG level is affected by both weight gain and age in FCHL. In younger Japanese children (7), type IIb was reported to be found in 0.26%, which was much lower than our result. However, the children with FCHL had already become obese in this study. Shamir *et al.* also reported that children with FCHL tended to be overweight (6). While the cause of obesity in FCHL patients is unknown, leptin is reported to be an indicator of energy metabolism that may be responsible for obesity seen in children with FCHL (14), because they have relatively higher leptin levels per body weight than children with FH. Furthermore, direct effects of leptin on insulin-stimulated glucose uptake in cultured rat skeletal muscle cells (15) suggested that leptin may also be responsible for development of glucose intolerance.

Kuromori *et al.* (3) reported that, in FCHL, a higher apoB level may be revealed antecedently at an early age without other lipid abnormality, and thus an elevated apoB level should be added to the early diagnostic criteria for FCHL in children. Shamir *et al.* (6) also reported that apoB

was not correlated with age in children with FCHL. In the 20-year prospective study of FCHL adults (11), elevated apoB was common among hyperlipidemic individuals from families with FCHL, and it might be useful for distinguishing unaffected relatives. Unfortunately we could not investigate apolipoproteins of participants in this study. However, they may have high apoB levels, because their LDLC levels were much higher (137–193 mg/dl) than the mean value in healthy Japanese children (63 mg/dl) (16).

FCHL was the most common form of familial hyperlipidemia in a referral population of children (4). We should establish an effective screening system and management program.

Conclusions

Our screening program detected 5 children with FCHL, with a prevalence of 0.4%. All of them demonstrated type IIa phenotype. Our results suggested that at least half of all individuals with FCHL already demonstrate a characteristic serum lipid profile in childhood. Effective medical intervention in these children is necessary to achieve primary prevention of CHD.

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References

- (1) Mabuchi H, Fujita H, Uno K, Inadu A, Kajinami K, Takeda M, Itou H, Kamon N, Koizumi J, Suematsu T, Shimizu T, and Takeda R: The frequency of familial hyperlipidemia and familial combined hyperlipidemia in myocardial infarction patients. *J Jpn Atheroscler Soc*, 16: 299, 1988 (In Japanese with English abstract)
- (2) Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG, Campbell ED, and Levinski MJ: Hyperlipidemia in coronary heart disease. II Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest*, 52: 1544–1568, 1973
- (3) Kuromori Y, Okada T, Iwata F, Hara M, Noto N, and Harada K: Familial combined hyperlipidemia (FCHL) in children: the significance of early development of hyperapoB lipoproteinemia, obesity and aging. *J Atheroscler Thromb*, 9: 314–320, 2002
- (4) Cortner JA, Coates PM, and Gallagher PR: Prevalence and expression of familial combined hyperlipidemia in childhood. *J Pediatr*, 116: 514–519, 1990
- (5) Cortner JA, Coates PM, Liacouras CA, and Jarvik

- GP: Familial combined hyperlipidemia in children: clinical expression, metabolic defects, and management. *J Pediatr*, 123: 177–184, 1993
- (6) Shamir R, Tershakovec AM, Gallagher PR, Liacouras CA, Hayman LL, and Cortner JA: The influence of age and relative weight on the presentation of familial combined hyperlipidemia in childhood. *Atherosclerosis*, 121: 85–91, 1996
- (7) Ohta T, Kiwaki K, Endo F, Umehashi H, and Matsuda I: Dyslipidemia in young Japanese children: its relation to familial hypercholesterolemia and familial combined hyperlipidemia. *Pediatr Int*, 44: 602–607, 2002
- (8) Investigating Committee of Guideline for Diagnosis and Treatment of Hyperlipidemias, Japan Atherosclerosis Society: Guideline for diagnosis and treatment of hyperlipidemia in adults. *J Jpn Atheroscler Soc*, 25: 1–34, 1997 (In Japanese with English abstract)
- (9) Nurata M: Guide-Line for treatment of hyperlipidemia in childhood. *J Jpn Atheroscler Soc*, 23: 631–636, 1996
- (10) Yamazaki K, Matsuoka H, Kawanobe S, Fujita Y, and Murata M: Evaluation of standard body weight by sex, age, and height – on the basis of 1990 school year data. *J Jpn Pediatr Soc*, 98: 96–102, 1994 (in Japanese with English abstract)
- (11) McNeely MJ, Edwards KL, Marcovina SM, Brunzell JD, Motulsky AG, and Austin MA: Lipoprotein and apolipoprotein abnormalities in familial combined hyperlipidemia: a 20-year prospective study. *Atherosclerosis*, 159: 471–481, 2001
- (12) Polonsky SM, Simbartl LA, and Sprecher DL: Triglyceride and high density lipoprotein cholesterol: predicting disorders in parents from their children. *Pediatrics*, 94: 824–831, 1994
- (13) Lapinleimu J, Nuotio IO, Lapinleimu H, Simell OG, Rask-Nissila L, and Viikari JS: Recognition of familial dyslipidemias in 5-year-old children using the lipid phenotypes of parents. The STRIP project. *Atherosclerosis*, 160:417–423, 2002
- (14) Jacobson MS, Yoon DJ, and Frank GR: Serum leptin is elevated out of proportion to the body mass index in adolescent females with familial combined hyperlipidemia (FCH). *Clin Pediatr*, 38: 49–53, 1999
- (15) Sweeney G, Keen J, Somwar R, Konrad D, Garg R, and Klip A: High leptin levels acutely inhibit insulin-stimulated glucose uptake without affecting glucose transporter 4 translocation in I6 rat skeletal muscle cells. *Endocrinology* 2001; 142: 4806–4812
- (16) Okada T, Sato Y, Yamazaki T, Iwata F, Hara M, Kim H, Karasawa K, Ayusawa M, Fuchigami T, Harada K, Okuni M, and Ryo S: Lipoprotein(a) and apolipoprotein A-1 and B in schoolchildren whose grandparents had coronary and cerebrovascular events: A preliminary study of 12-13 year old Japanese children. *Acta Paediatr Jpn*, 37: 582–587, 1995