Efficacy of Targeted Screening for Childhood Hypercholesterolemia in Japan

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Summary: The aim of this study is to evaluate the efficacy of targeted screening on the basis of the results from the universal screening of Japanese children. A total of 698 children consisting of 348 in the 3rd grade of elementary school (third graders) and 350 in the 3rd grade of junior high school (ninth graders) were enrolled in one local school district, during the period 1985 to 1998. When body mass index was used as the sole indicator, the sensitivity in detecting hypercholesterolemia was 14.3% in the case of third graders, and 14.7% in that of ninth graders. Family history was investigated through a questionnaire inquiring about the history of 6 atherosclerosis-related diseases in 6 relatives. The sensitivity on the basis of family history was calculated as 0% to 54.5%. According to the atherosclerotic index calculated from the measured levels of total and HDL cholesterol, sensitivity of abnormal levels of atherosclerotic index in children was almost the same as those of hypercholesterolemia. Using targeted screening, it was possible to detect only around half or less of the subjects with hypercholesterolemia. With respect to the sensitivity of the screening, universal screening is recommended for detecting hypercholesterolemia in Japanese children.

Key words child, cholesterol, universal screening, targeted screening, atherosclerotic disease

INTRODUCTION

A significant correlation can be seen between blood cholesterol level that tends to increase in association with a Western-style diet and atherosclerosis. Along with changes in dietary habits, risk factors to atherosclerotic diseases, such as obesity and hyperlipidemia, have been noted in Japanese children, which could lead to the occurrence of this disease at a young age.

Risk factors of atherosclerosis include hyperlipidemia, diabetes mellitus, hypertension, obesity, smoking, family history of vascular disease, insufficient exercising and stress. It is important to identify which of these factors can be eliminated and to reduce and eliminate them at the earliest possible stage to prevent future development of the disease in the child, and to improve his (her) quality of life

during the rest of his (her) life.

Universal screening and targeted screening are used to detect one of the above-mentioned cardiovascular risk factors, i.e., hyperlipidemia. The former is a mass screening method in which the serum lipids of all subjects are screened, while the latter is a selective screening method in which those who have risk factors of atherosclerosis themselves or whose family has such risk factors are selected, and only the serum lipids of those subjects who are at risk are screened [1,2]. Considering the economic and psychological burdens borne by the subjects, targeted screening may be better, because primary screening is conducted according to a method which causes few inconveniences to the subjects, such as a questionnaire, and then blood tests are carried out as the secondary screening only in the children shown to be at risk by the primary screening. However, the

efficacy of targeted screening is unknown, and there have been no comparative reports on the efficacy of these two screening methods in Japan.

The aim of this study is to evaluate the efficacy of targeted screening for hypercholesterolemia using several risk factors on the basis of the results of universal screening in Japan.

MATERIALS AND METHODS

Subjects

Regular health check-up and questionnaire surveys were conducted in May or June every year for all children attending all elementary schools and junior high schools in one school district in Hokkaido, northern Japan. Findings from the 14 years from 1985 to 1998 were available and were kindly provided to this study. Their guardians had consented to the screening. In this study, the results of measurements and questionnaires obtained from students in the 3rd grade of elementary school (3rd graders: 9 to 10 years old) and students in the 3rd grade of junior high school (9th graders: 14 to 15 years old) were investigated to evaluate the efficacy of targeted screening (Table 1). Blood specimens were collected from 83.9% of the 3rd graders, and 85.2% of the 9th graders.

Details of health check-up

Body height and body weight were measured, and the body mass index (BMI) was calculated. Obesity was defined as a BMI higher than the 90 percentile value (3rd graders: BMI 21.3; 9th graders: BMI 25.0).

Blood specimens were collected in the morning before lunch at school. The total cholesterol level

was determined by an enzymatic method. Hypercholesterolemia was defined as a serum total cholesterol (TC) level higher than the 90 percentile value (3rd graders: 202 mg/dl; 9th graders: 196 mg/dl). Hypo-HDL cholesterol was defined as HDL cholesterol level lower than the 10 percentile value (3rd graders: 43 mg/dl; 9th graders: 40 mg/dl). The atherosclerotic index was obtained by the following equation: (total cholesterol – HDL cholesterol)/HDL cholesterol. Values higher than the 90 percentile value (3rd graders: 2.86; 9th graders: 2.94) were regarded as not normal.

The family history of 6 relatives (parents, and grandparents on both sides) were examined. The presence or absence of a history of 6 atherosclerosis-related diseases, i.e., hypertension, diabetes mellitus, hypercholesterolemia, angina, myocardial infarction and apoplectic stroke, was surveyed using a pre-coded questionnaire. The mean ages of the parents of the subjects were as follows: fathers of 3rd graders: 39.2 ± 4.4 years, mothers of 3rd graders: 36.5 ± 3.7 years, fathers of 9th graders: 44.9 ± 4.5 years; and mothers of 9th graders: 41.5 ± 3.9 years.

Data analysis

SPSS (SPSS Inc., Chicago, IL, version 6.0j for Windows) was used for statistical analysis, and student's t-tests were used for inter-group comparisons. The test was conducted as a two-tailed t-test, and the level of significance was set at 5%.

RESULTS

Body build

The body heights and body weights of all children in 3rd and 9th grades are presented in Table 1

TABLE 1.
Characteristics of the study population

	3rd graders		9th graders	
	male 169	Female 179	male 170	Female 180
/N				
Height (cm)	128.8 $\pm$ 5.2	** 127.4 $\pm$ 5.0	165.9 $\pm$ 5.7	*** 155.8 $\pm$ 4.7
Body Weight (kg)	29.1 $\pm$ 5.9	*** 27.2 $\pm$ 5.7	57.6 $\pm$ 10.5	*** 50.6 $\pm$ 7.5
Body Mass Index	17.4 $\pm$ 2.6	*** 16.6 $\pm$ 2.5	20.9 $\pm$ 3.4	20.9 $\pm$ 3.2
Total Cholesterol (mg/dl)	170.0 $\pm$ 26.1	169.7 $\pm$ 26.0	151.2 $\pm$ 25.7	*** 167.2 $\pm$ 26.4
HDL-Cholesterol (mg/dl)	58.1 $\pm$ 11.0	56.4 $\pm$ 13.1	51.8 $\pm$ 10.8	*** 56.4 $\pm$ 12.0
Atherosclerotic index	2.0 $\pm$ 0.7	2.1 $\pm$ 0.7	2.0 $\pm$ 0.8	2.1 $\pm$ 0.7

male vs. female; **p < 0.01, ***p < 0.001

by grade and by gender. The body height and body weight were significantly higher in boys than in girls. BMI was significantly higher in boys than in girls among 3rd graders, while there was no significant difference between boys and girls in 9th grade.

The serum lipid

Mean values of blood biochemical parameters are also shown in Table 1. The serum total cholesterol level and HDL cholesterol level in girls were significantly higher than in boys in the 9th grade, but no significant differences were noted between boys and girls in the 3rd grade. There was no significant difference in the atherosclerotic index between grades, nor between boys and girls. The serum total cholesterol level and HDL cholesterol level were significantly higher in 3rd graders.

BMI as the screening indicator

As shown in Table 2 when targeted screening was conducted on obese children, the sensitivity in detecting hypercholesterolemia was 14.3% in the case of 3rd graders and 14.7% in that of 9th graders. The specificity was high (90.7% and 89.6%, respectively). When the high atherosclerotic index was used in the calculation, sensitivity was 26.5% in the

case of the 3rd graders, and 40.0% in that of the 9th graders.

Family history as the screening indicator

The results obtained by the 6 relatives are shown in Table 3. If at least one disease was present, the subject was regarded as having a risk factor. The sensitivity in detecting hypercholesterolemia in their children varied from 0% (mother) to 33.3% (grandmother on the father's side) in the case of the 3rd graders, and from 5.9% (mother) to 17.6% (grandmother on both sides) in that of the 9th graders.

A screening indicator was defined as at least one of the 6 relatives having one of the 6 diseases (Table 4). When a family history of hypercholesterolemia was used as the screening indicator, the sensitivity was low (21.2% in the case of 3rd graders and 11.8% in that of 9th graders). The sensitivity in detecting a high atherosclerotic index varied from 0 to 37.9%, and was almost the same as that in detecting hypercholesterolemia.

When at least one of the 6 relatives who had one of the 6 diseases was considered as a screening indicator, the efficacy of this approach was examined (Table 5). The sensitivity in the case of the 3rd graders was 54.5%, while in the 9th graders it was

TABLE 2.
Sensitivity and specificity of total cholesterol and atherosclerotic index in identifying with obesity

	Total cholesterol		Atherosclerotic index	
	SENS	SPEC	SENS	SPEC
3rd graders	14.3	90.7	26.5	92.0
9th graders	14.7	89.6	40.0	92.4

SENS: sensitivity; SPEC: specificity

TABLE 3.
Sensitivity and specificity of total cholesterol and atherosclerotic index in identifying with family history

	Total cholesterol				Atherosclerotic index			
	3rd graders		9th graders		3rd graders		9th graders	
	SENS	SPEC	SENS	SPEC	SENS	SPEC	SENS	SPEC
Father	3.0	92.4	8.8	91.6	6.9	92.9	5.7	91.3
Paternal grandfather	3.0	75.1	17.6	81.4	6.9	75.8	11.4	80.6
Paternal grandmother	33.3	71.9	17.6	74.9	20.7	70.6	22.9	75.5
Mother	0.0	97.1	5.9	94.5	0.0	97.2	2.9	94.2
Maternal grandfather	21.2	76.3	14.7	80.4	20.7	76.2	14.3	80.4
Maternal grandmother	21.2	72.3	8.8	75.6	24.1	72.7	17.1	76.5

SENS: sensitivity; SPEC: specificity

TABLE 4.
Sensitivity and specificity of total cholesterol and atherosclerotic index in identifying with family history of atherosclero-related diseases

	Total cholesterol				Atherosclerotic index			
	3rd graders		9th graders		3rd graders		9th graders	
	SENS	SPEC	SENS	SPEC	SENS	SPEC	SENS	SPEC
Hypertension	36.4	54.9	29.4	55.6	37.9	55.2	40.0	56.8
Diabetes	15.2	80.9	17.6	83.6	20.7	81.5	11.4	82.9
Myocardial infarction	3.0	92.1	2.9	90.0	0.0	91.8	8.6	90.6
Angina	9.1	93.5	8.8	95.5	3.4	92.9	0.0	94.2
Stroke	6.1	93.5	2.9	93.2	10.3	94.0	2.9	93.2
Hypercholesterolemia	21.2	72.3	11.8	95.5	24.1	72.7	11.4	95.5

SENS: sensitivity; SPEC: specificity

TABLE 5.
Sensitivity and specificity of total cholesterol and atherosclerotic index in identifying with family history of any atherosclero-related diseases

	Total cholesterol		Atherosclerotic index	
	SENS	SPEC	SENS	SPEC
3rd graders	54.5	39.7	48.3	39.0
9th graders	47.1	43.7	48.6	43.9

SENS: sensitivity; SPEC: specificity

47.1%. As to the atherosclerotic index, the sensitivity in the case of the 3rd graders was 48.3%, showing almost no differences, but in that of the 9th graders it was 48.6%.

DISCUSSION

Prospective epidemiologic studies of risk factors to atherosclerosis in children have been actively conducted in Western countries. In particular, the Bogalusa Heart Study has demonstrated an obvious correlation between the spread of fatty streaks and fibrous plaques in the coronary arteries of patients who died young, and the antemortem risk factors, such as hyperlipidemia and systolic blood pressure [3]. The same may be true in Japanese young people, because a nationwide study of atherosclerosis in infants, children and young adults showed fatty streaks and fibrous plaques were observed in the coronary arteries and even in the aorta of an infant under 1 year of age [4]. While rapid westernization of dietary habits is progressing in Japan, there have been only a few reports on cholesterol-level screen-

ing of children [5,6]. Therefore, more attention should be paid to cardiovascular risk factors including hyperlipidemia and obesity on a national level in Japan, and guidelines, as in the United States, need to be formulated.

When detection of hypercholesterolemia in children was attempted on the basis of their family history as obtained by questionnaire survey regarding the presence or absence of 6 atherosclerosis-related diseases in 6 relatives, the sensitivity was low (from 0% to 54.5%). A similar tendency was observed when the atherosclerotic index calculated from measurements of HDL cholesterol levels was used. The results of our present study indicated that it is impossible to screen children efficiently for hypercholesterolemia on the basis of their body build and their family history.

Two methods are available for screening, i.e., universal screening and targeted screening, and the efficacy of these methods is controversial [1,2]. The National Cholesterol Education Program (NCEP) and the American Academy of Pediatrics (AAP) have recommended a selective approach to only

those children with a family history of two conditions which are considered to increase the risk of development of ischemic heart disease in the child concerned, in other words, a history of premature vascular disease at an age younger than 55 years in the child's parents or grandparents, or hyperlipidemia of 240 mg/dl or more in the child's parents or brothers or sisters [7]. This is because there is evidence that the cholesterol level tends to be high in children who have family members with hyperlipidemia [8,9], and that ischemic heart disease and hyperlipidemia are likely to be accumulated in a family [10,11]. On the other hand, some researchers criticize the selective approach [11-13]. Primrose et al. [1] investigated the efficacy of selective screening of children for hyperlipidemia according to the presence or absence of family history (history of angina and myocardial infarction in parents, grandparents, and uncles or aunts 55 years old or younger) in adolescents 12 to 15 years old. According to them, the sensitivity of the approach was 33.2% and specificity was 71.5%, suggesting that hyperlipidemia may be overlooked in two-thirds of the children. Thus, they concluded that the approach was not effective. Our study also suggested poor sensitivity of the approach using the family history. When the family history of hypercholesterolemia was used as the screening indicator, the sensitivity was extremely low (21.2% in the 3rd graders, and 24.1% in the 9th graders).

One of the causes of poor sensitivity may be the reliability of family history obtained by questionnaire. Resnicow et al. [14] pointed out that a history of parental hypercholesterolemia, which was used as the rationale for the guidelines of AAP and NCEP, was reliable because it was obtained on the basis of actually determined cholesterol levels of the parents. Therefore, the conclusion drawn by numerous reports including our present report that prediction of hypercholesterolemia in children on the basis of family history is impossible may be partially explained by the low reliability of the self-reported cholesterol value obtained by questionnaires. This was also a problem in Japan where parents may need further education. One possible reason is that cholesterol screening in adults is not functioning sufficiently, and many adults have not had their cholesterol level measured, or do not remember their cholesterol levels. Moreover, the questionnaire on the family history did not ask the exact cholesterol level, but unspecifically asked parents for the presence or absence of hypercholesterolemia. Therefore, some respondents might have known their cholesterol level

but had difficulty in judging whether the level meant hyperlipidemia. The same problem applies to family history of hypertension. Thus, to increase the efficacy of selective screening based on family history, Diller et al. [2] adopted such factors as hypertension, obesity, and the consumption of a fat-rich and cholesterol-rich diet, in addition to the above-mentioned two major indicators proposed by the Expert Panel for NCEP for Children and Adolescents. They reported that employment of additional discretionary and major indicators enabled the identification of 96% of hyper-LDL cholesterol, and suggested the necessity of examining multiple screening indicators. In our study, however, we investigated the obesity and hypertension of the subjects themselves in addition to the family history, but sensitivity was still low.

It is controversial which factors should be determined for predicting the development of atherosclerosis in the future. The Muscatine Study, Lauer et al. [15] investigated whether the development of hypercholesterolemia in adulthood can be predicted by hypercholesterolemia in childhood. According to their study, it was difficult to predict future development of hypercholesterolemia in adulthood in individual subjects on the basis of high cholesterol levels obtained by two measurements in childhood. Moreover, the cholesterol level became normal when the child reached adulthood in the majority of cases. Thus, they were wary of the benefits of universal screening. As a reason for this, they suggested that the total cholesterol level in childhood may not reflect the LDL cholesterol level. This means that screening based on levels of total cholesterol alone does not allow the selection of those at high risk in a true sense. Rifai et al. [16] reported that it is possible to predict hyper-LDL cholesterol in 100% of subjects by adding HDL cholesterol to the screening factors. We determined the HDL cholesterol level in addition to the total cholesterol level, and determined the sensitivity and specificity of the atherosclerotic index calculated from the HDL cholesterol level, but the sensitivity and specificity of screening were similar to those used to detect hypercholesterolemia. LDL cholesterol levels are usually calculated from the cholesterol, HDL cholesterol, and triglyceride levels. Recently, however, direct measurement of the LDL cholesterol level has become possible. Investigation of the effectiveness of determination of the LDL cholesterol level alone, instead of the total cholesterol level, will be necessary in the future, while considering the issue of cost.

We concluded that the detection of people with high cholesterol levels by targeted screening is extremely problematic in Japan. The serum total cholesterol level is believed to be affected by various factors, in addition to genetic and family environmental factors, and universal screening seems to be better in terms of sensitivity. However, this conclusion is drawn from a study on 3rd graders who are in early childhood, and 9th graders who are in the midst of adolescence. Even if universal screening is to be adopted to help prevent atherosclerosis, numerous problems remain to be solved, including the appropriate age for screening, and the appropriate intervals between the tests. It is necessary to choose a method that is optimal for the purpose of the screening, after carefully considering the advantages and disadvantages of various methods.

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