SERUM HDL-CHOLESTEROL AND LIPOPROTEIN FRACTION IN KAWASAKI DISEASE (ACUTE MUCOCUTANEOUS LYMPH NODE SYNDROME)

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Serum HDL-cholesterol level and lipoprotein fraction were studied in 50 patients with Kawasaki disease (acute mucocutaneous lymph node syndrome), ranging in age from 4 months to 7 years, with an average of 2 years and 6 months. There were 31 males and 19 females. In 7 of these patients coronary arterial aneurysms were revealed by aortogram. In all 50 patients analysis were carried out periodically from the onset of the disease to the convalescent stage, and the following results were obtained: 1) Serum total cholesterol level showed mild change throughout the course of the disease. 2) Average HDL-cholesterol level was 29.6 ± 11.0 mg/dl in the first week of the disease, 26.8 ± 8.9 from 1 to 2 weeks and 47.9 ± 12.6 after 6 weeks. There was significant difference between the HDL-cholesterol levels of first 2 weeks and after 4 weeks ($p < 0.01$). 3) The recovery of HDL-cholesterol level was slow in both clinically severe patients and the patients with coronary aneurysms as compared with that in clinically mild patients ($p < 0.05$).

These findings suggest that there may be some relationships between the alteration of serum lipoprotein and the severity of systemic vasculitis in Kawasaki disease, especially which may play some role in clinical severity and the occurrence of coronary arterial lesions. However, further study is needed to clarify the cause of changes in serum HDL-cholesterol and lipoprotein.

KAWASAKI disease (acute febrile mucocutaneous lymph node syndrome) is an acute inflammatory disease, consisting mainly of systemic vasculitis and commonly affecting infants and young children. It is characterized by panarteritis which occurs mostly in the coro-

nary arteries and also it is accompanied by aneurysms of the coronaries^{1,2} as a sequella of the disease. It has been reported that 44%¹ or 51%² of the deaths occurred within 4 weeks from the onset of the disease. In most cases, myocarditis, thrombus formation in coronary aneurysms and stenosis of the coronary arteries have been demonstrated by autopsy. This severe pathological condition which takes place in a relatively short period is also one of the characteristics of Kawasaki disease and it is rare in

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TABLE I SEVERITY OF ILLNESS AND COMPLICATIONS IN FIFTY PATIENTS WITH KAWASAKI DISEASE

	No complication	Coronary aneurysm	Distended gallbladder
Mild cases	28/31	0/31	3/31
Moderate cases	6/10	2/10	2/10
Severe cases	3/9	5/9	1/9
Total	37/50	7/50	6/50

TABLE II PROCEDURE FOR HDL-CHOLESTEROL MEASUREMENT

Serum	1.0 ml
	1) 4,000 U heparin 40 micro liter
	2) 2.0 M/L MnCl ₂ 50 micro liter
	3) mix and centrifuge 15 min, at 3000 rpm
Supernatant	Precipitate
	4) transfer 20 μ l of upper layer to tube
	5) add to 3.0 ml of enzymatic reagent
	6) mix and incubate 15 min at 37°C
	7) spectrophotometrically read color intensity at 505 nm

other acute inflammatory diseases.

In recent years, lipoprotein metabolism has been studied in some kinds of vascular disease in adult patients. The present study was designed to investigate the changes of lipoprotein as a coronary risk factor in Kawasaki disease from the view point of vascular disease.

MATERIALS AND METHODS

Fifty patients (31 males and 19 females) with Kawasaki disease were studied. Their ages ranged from 4 months to 7 years, averaging 2 years and 6 months. The patients were divided into three groups according to Asai's scoring system,³ which was established to estimate the degree of each clinical manifestation and laboratory finding and to express the severity of the disease in its entirety. Five points or less were evaluated as mild cases, 6 to 8 points as moderate cases and 9 points or more as severe cases (Table I). The following 2 complications were observed in 13 of the 50 patients: coronary aneurysms were demonstrated angiographically in 7 patients and distended gallbladder was proved by ultrasound examination in the remaining 6 patients. There was no fatal case in this series.

The following 4 items were examined weekly from the onset of the disease until recovery:

Serum total cholesterol was measured by the

enzymatic method. The procedure was checked by the study group supported by the Ministry of Health and Welfare, Japan and the result of blind checking was within permissible range.

HDL (high density lipoprotein)-cholesterol was measured by means of the heparin-manganese method (Table II).

The value of [VLDL (very low density lipoprotein) + LDL]-cholesterol was obtained by subtracting HDL-cholesterol value from serum total cholesterol one.

In addition the changes of the ratio of HDL-cholesterol to [VLDL + LDL]-cholesterol were investigated.

The normal values of serum total cholesterol and HDL-cholesterol in our institute were 159.0 ± 40.7 and 49.2 ± 12.5 mg/dl respectively, which were obtained from 11 normal subjects, ranging in age from 1 to 7 years and averaging 4 years and 2 months.

RESULTS

The changes of serum total cholesterol, HDL-cholesterol, [VLDL + LDL]-cholesterol and the ratio of HDL-cholesterol/[VLDL + LDL]-cholesterol in 50 patients during the course of the disease are shown in Fig. 1. The total amount of serum cholesterol was lower than the normal value in the first week of the illness, but increased

Fig. 1. Weekly variations of serum total cholesterol, HDL-cholesterol, [VLDL + LDL]-cholesterol and HDL-cholesterol/[VLDL + LDL]-cholesterol in patients with Kawasaki disease. Parentheses indicate the number of cases.

from the 2nd to the 4th week and returned to normal range after 6 weeks. Serum HDL-cholesterol was extremely lower than the normal range within the first 2 weeks, but then increased gradually with the recovery from the illness. In the first 2 weeks [VLDL + LDL]-cholesterol decreased but not so sharply as HDL-cholesterol. It showed a rebound elevation from the 2nd to the 4th week and during the following 4 weeks it returned to the normal range. There was a relationship between the increase of [VLDL +

LDL]-cholesterol and the reduction of HDL-cholesterol during the first to the 2nd week.

Periodical percent variations of HDL-cholesterol and [VLDL + LDL]-cholesterol as compared with the values in the recovery phase are shown in Fig. 2, which revealed clearly the weekly variations of the serum lipoprotein fractions. Serum total cholesterol decreased during the first week of the illness mainly due to a reduction of HDL-cholesterol, and increased during the 2nd to the 4th week mainly as a

Fig. 2. Periodical percent variation of HDL-cholesterol and [VLDL + LDL]-cholesterol as compared with the values at recovery phase 6 weeks after the onset of the illness.

result of the rebound elevation of [VLDL + LDL]-cholesterol rather than the recovery of HDL-cholesterol during the same period. HDL-cholesterol was persistently low in the group with coronary arterial aneurysm as well as in the severe group; it was significantly lower in the former than in the mild group even in the 4th week.

The ratio of HDL-cholesterol to [VLDL + LDL]-cholesterol was low in the first 2 weeks and gradually increased in accordance with the recovery from the illness. HDL-cholesterol also showed the same pattern as the change of this ratio, and both correlated with the clinical severity of the disease (Figs. 1 and 3).

Figure 3 shows the difference of serum lipoprotein cholesterol among the 5 groups classified according to the three severity categories of the illness³ and the two complications. Although serum lipoprotein cholesterol changed in a similar manner in all groups, the following exceptions were noted: In the first week of the illness, HDL-cholesterol reduced more prominently in the group with distended gallbladder than in the other groups, but recovered consider-

ably afterwards. In patients with coronary arterial aneurysm as well as in the severe group, however, HDL-cholesterol showed a relatively poor recovery; it was significantly lower than that in the other groups even 4 weeks after the onset of the illness ($p < 0.05$). Similarly, there was a significant statistical difference ($p < 0.05$) between these two groups and other groups in the ratio of HDL-cholesterol to [VLDL + LDL]-cholesterol. On the other hand, serum total cholesterol and [VLDL + LDL]-cholesterol didn't show any significant statistical difference among the 5 groups.

DISCUSSION

This study presented a remarkable change in lipoprotein metabolism in the patients with Kawasaki disease. HDL-cholesterol decreased and [VLDL + LDL]-cholesterol increased in the acute phase of Kawasaki disease. Serum total cholesterol also changed according to the variations of HDL-cholesterol and [VLDL + LDL]-cholesterol. The explanation of these findings is not clear, but the condition characterized by the lowering of HDL (an antiarteriosclerotic factor) and by the elevation of LDL (an arteriosclerosis promoting factor) is probably an invasive risk factor to vascular walls.

Interestingly, these alterations in lipoprotein metabolism in the acute phase of Kawasaki disease coincided with hematological changes, such as increased platelets and hypercoagulability⁴ and pathological changes, such as degenerations of the endothelium and media of vascular walls². The relationship of these findings may be explained by both the 'endothelial injury-platelet aggregation hypothesis' and 'lipid infiltration hypothesis'. The change of lipoprotein metabolism may in part play a role in the genesis of aneurysm and thrombus formation, and in the further development of arterial changes.

A decrease in HDL-cholesterol and an increase in LDL-cholesterol in Kawasaki disease are probably due to systemic vasculitis, the cardinal manifestation of the disease, although true cause of these changes still remain obscure.

The influence of aspirin treatment and diet on lipoprotein metabolism should be considered. However, no substantial change by medical management occurred in this series from the onset to the convalescence. We believe that the sequential changes of lipoprotein fractions are essential occurrences in Kawasaki disease.

Fig.3. Difference of the mean values of serum total cholesterol, HDL-cholesterol, [VLDL + LDL]-cholesterol and HDL-cholesterol/[VLDL + LDL]-cholesterol in the 5 groups with Kawasaki disease.

Miller et al. observed a decrease in HDL in patients with ischemic heart disease⁵ Therefore, the long-sustained alteration of lipoprotein metabolism is considered likely to become a risk factor in the further development of coronary arteriosclerosis. This is partly supported by the evidence obtained from the specimens of coronary aneurysm removed by autopsy or during surgery. The previous pathological studies of the

coronary arterial walls in Kawasaki disease revealed a proliferation of the endothelium, intimal thickening, stenosis, calcification and other arterial changes.^{2,6}

We may conclude that systemic vasculitis gives rise to the inflammation of viscera, such as hepatitis, which disturbs HDL synthesis, leading to an impairment of LDL catabolism within the cells in the peripheral tissues, e.g., vascular walls,

and eventually resulting in the increase of LDL-cholesterol.

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