Coronary Artery Disease and Infection with Chlamydia Pneumonia

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SUMMARY

The association between chlamydia pneumonia and coronary artery disease is well documented, however less is known about the correlation between chlamydia pneumonia infection and blood inflammatory markers or lipid levels. In 100 patients with proven coronary artery disease (25 females, 61.0 ± 4.0 years old), and 60 healthy volunteer control cases (15 females, 60.6 ± 3.4 years old), anti chlamydia pneumonia IgG, blood lipid, C-reactive protein and fibrinogen levels were detected. In cases with coronary artery disease seropositivity for IgG antibodies to chlamydia pneumonia (74% versus 34%, $p < 0.0001$), C-reactive protein (mg / *l*) (2.8 ± 0.6 versus 1.4 ± 0.6, $p < 0.0001$), fibrinogen (mg / d*l*) (317.4 ± 38.2 versus 256.2 ± 34.5, $p < 0.0001$), triglyceride (mg / d*l*) (217.5 ± 39.0 versus 191.0 ± 25.9, $p < 0.0001$), LDL-cholesterol (mg / d*l*) (126.9 ± 19.2 versus 110.6 ± 19.5, $p < 0.0001$) levels and total cholesterol / HDL-cholesterol ratio (7.7 ± 1.8 versus 4.4 ± 1.2, $p < 0.0001$) were higher but the level of HDL-cholesterol (mg / d*l*) (26.4 ± 6.7 versus 47.0 ± 11.2, $p < 0.0001$) was lower. The levels of total cholesterol did not differ between the two groups ($p = 0.9$). Levels of triglyceride ($r = 0.60$, $p < 0.00001$), LDL-cholesterol ($r = 0.27$, $p = 0.0004$), C-reactive protein ($r = 0.69$, $p < 0.00001$), fibrinogen ($r = 0.60$, $p < 0.00001$) and total cholesterol / HDL-cholesterol ratio ($r = 0.74$, $p < 0.00001$) had a direct relation, but the level of HDL-cholesterol had a negative ($r = -0.80$, $p < 0.00001$) relation with the seropositivity for chlamydia pneumonia.

As a result, seropositivity for IgG antibodies to chlamydia pneumonia is considered as a risk factor for coronary artery disease by its association with the atherogenic lipid profile and procoagulant activity. (Jpn Heart J 2000; 41: 165-172)

Key words: Chlamydia pneumonia, Coronary artery disease, Blood lipids, Inflammatory markers.

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CHLAMYDIA pneumonia has been associated with coronary artery disease and myocardial infarction in several seroprevalence studies,[1-7] and one prospective cohort study.[8] This link has become more persuasive by the identification of chlamydia pneumonia (CP) elementary bodies in atherosclerotic plaques and fatty streaks in autopsy cases from the aorta and coronary arteries[9,10] from coronary atherectomy[11] and from endarterectomy specimens from carotid arteries.[12,13] The organism is rarely found in vascular specimens from non-atherosclerotic patients or those with nonatherogenic arteriopathy.[11,13-19]

Various mechanisms have been suggested whereby infection with CP may affect the risk of cardiovascular disease. Animal models have shown that CP easily gains access to the vascular system following pulmonary infection.[20] Infection of endothelial or smooth muscle cells in vessel walls may occur[21] resulting in local inflammation and fibrosis and subsequent atheroma formation. Alternatively repeated or persistent CP infection may stimulate the production of proinflammatory cytokines[22] which may increase the risk of cardiovascular disease[23,24] by disturbing the basal thromboresistant function of vascular endothelial cells[25] inhibiting endothelium derived relaxing factor,[25,26] or affecting smooth muscle cell contractility[27] or induction of an atherogenic lipid profile.[28,29]

In this prospective case controlled study blood samples of patients with coronary artery disease (CAD) were analysed for the presence of IgG antibodies against CP and its relation with levels of blood lipids and inflammatory markers was studied.

MATERIALS AND METHODS

We studied 100 consecutive patients with angiographically proven coronary artery disease (25 females, ages 61.0 ± 4.0 years) and all were stable at the time of study. The control group consisted of 60 healthy volunteers (15 females, ages 60.6 ± 3.4 years). Their ages, all gender, body mass indexes, smoking and alcohol habits were well matched to each other. All of the patients had angiographic documentation of a coronary stenosis ≥ 50 % of at least one coronary artery, and all without recent or remote myocardial infarction. The control group was chosen from healthy volunteers not having any cardiac or inflammatory disease. All underwent total blood count, resting electrocardiography and exercise stress electrocardiography to exclude any inflammatory or ischemic heart disease.

Exclusion criteria included: Recent myocardial infarction, stable or unstable angina pectoris, an immunological disease, and an infectious or inflammatory disease in the last 6 months, liver insufficiency, primary myocardial disease, and endomyopericarditis.

Height and weight were measured and body mass index (BMI) determined, a blood sample (not fasting) taken, centrifuged and separated within four hours. Serum from all subjects was analysed for total cholesterol (by an enzymatic colorimetric method), HDL-cholesterol (by a lipoprotein precipitation method), triglycerides (TG) (by an enzymatic colorimetric method), LDL-cholesterol (calculated according to Fridewald formula) and C-reactive protein (CRP) levels. Plasma was analysed for fibrinogen levels (photo-optically). The ratio of total cholesterol to HDL-cholesterol was then determined. Serum from all cases was analysed for the presence of anti CP antibodies. The chlamydia MIF (microimmunofluorescence) assay was used to detect the presence of IgG antibodies to antigens from CP at a serum dilution of 1: 64.

Statistics: Analysis was done using a 2-sample independent-t test and chi-square test for comparison of 2 groups. Pearson's correlation analysis was used to show the relation between variables and anti CP IgG seropositivity and presence of coronary artery disease. A p value of < 0.05 was accepted as statistically significant.

RESULTS

The demographic variables of the groups are shown in Table I. This report was based on sera from 160 subjects, 100 of whom were patients with proven CAD at the stable and chronic stage and 60 were healthy volunteers. Seropositivity for anti CP IgG was 78 % for the patient and 34 % for the control groups ($p < 0.0001$) (Table II) and were not correlated with age, sex, BMI, blood pressure levels, smoking habit or alcohol consumption.

In the CAD group TG (mg / dl) (217.5 ± 39.0 versus 191.0 ± 25.9, $p < 0.0001$), LDL-cholesterol (mg / dl) (126.9 ± 19.2 versus 110.6 ± 19.5, $p < 0.0001$), CRP (mg / l) (2.8 ± 0.6 versus 1.4 ± 0.6, $p < 0.0001$), and fibrinogen (mg / dl) (317.4 ± 38.2 versus 256.2 ± 34.5, $p < 0.0001$) levels and the total cholesterol / HDL-cholesterol ratio (7.7 ± 1.8 versus 4.4 ± 1.2, $p < 0.0001$) were higher than the control cases, but the level of HDL-cholestorol (mg / dl) (26.4 ± 6.7 versus 47.0 ± 11.2, $p < 0.0001$) was lower. The level of total cholesterol did not differ between the groups ($p = 0.9$) (Table II). While the levels of TG ($r = 0.60$, $p < 0.00001$), LDL-cholesterol ($r = 0.27$, $p = 0.0004$), CRP ($r = 0.69$, $p < 0.00001$), and fibrinogen ($r = 0.60$, $p < 0.00001$) and the total cholesterol / HDL-cholesterol ratio ($r = 0.74$, $p < 0.00001$) showed a direct relation with the presence of anti CP IgG antibody, the HDL-cholesterol level showed an inverse relation ($r = -0.80$, $p < 0.00001$). We also observed a positive relation for TG ($r = 0.34$, $p < 0.0001$), LDL-cholesterol ($r = 0.38$, $p < 0.0001$), CRP ($r = 0.73$, $p < 0.0001$), fibrinogen ($r = 0.62$, $p < 0.0001$), and total cholesterol / HDL-cholesterol

Table I. Baseline Characteristics of the Study Groups

Variables	CAD ($n = 100$)	Control ($n = 60$)	p
Age (years)	61.0 ± 4.0	60.6 ± 3.4	0.5
Gender (% female)	25	25	1
BMI (kg / m^2)	24.9 ± 1.4	24.7 ± 1.4	0.5
Smoking ratio (%)	42	36	0.53
Alcohol (%)	8	3	0.4
Hypertension (%)	35	0	< 0.0001
Diabetes mellitus (%)	20	0	< 0.0001
Hypertension ± Diabetes mellitus (%)	13	0	< 0.0001
Systolic blood pressure (mmHg)	129.1 ± 17.5	118.0 ± 8.6	< 0.0001
Diastolic blood pressure (mmHg)	78.9 ± 10.7	72.9 ± 5.7	< 0.0001

Table II. Laboratory Findings of the Study Groups

Variable	CAD ($n = 100$)	Control ($n = 60$)	p
Anti CP IgG seropositivity (%)	74	34	< 0.0001
Total cholesterol (mg / d*l*)	196.7 ± 20.0	196.0 ± 21.0	0.9
HDL-cholesterol (mg / d*l*)	26.4 ± 6.7	47.0 ± 11.2	< 0.0001
LDL-cholesterol (mg / d*l*)	126.9 ± 19.2	110.6 ± 19.5	< 0.0001
TG (mg / d*l*)	217.5 ± 3.9	191.0 ± 25.9	< 0.0001
Total cholesterol / HDL	7.7 ± 1.8	4.4 ± 1.2	< 0.0001
CRP (mg / *l*)	2.8 ± 0.6	1.4 ± 0.6	< 0.0001
Fibrinogen (mg / d*l*)	317.4 ± 38.4	256.2 ± 34.5	< 0.0001

($r = 0.70$, $p < 0.0001$), and a negative relation for HDL-cholesterol ($r = -0.75$, $p < 0.0001$) with the presence of CAD (Table III). The correlations between variables in the presence of anti CP IgG antibodies according to the presence or absence of CAD are presented in Table IV. Similar correlations for the variables in the two different groups for the presence of anti CP IgG antibodies were observed. In other words, positive correlations for TG, LDL-cholesterol, CRP, fibrinogen, total / cholesterol / HDL - cholesterol, and a negative relation for HDL-cholesterol with the presence of anti CP IgG antibodies were observed in the two groups.

DISCUSSION

The ability of several microorganisms (*Helicobacter pylori*, *Chlamydia pneumonia* and the agents of dental infections) to cause chronic infections and to be related to both CAD and cardiovascular risk factors has been recently proved.[5)]

Chronic CP infection might contribute to the development of coronary heart

Table III. Correlations between Laboratory Findings and Anti CP IgG Seropositivity and CAD According to Pearson's Correlation Analysis

Variable		Anti CP IgG seropositivity	CAD
Total Cholesterol	*r*	− 0.01	0.007
	p	0.83	0.92
HDL-cholesterol	*r*	− 0.80	− 0.75
	p	< 0.00001	< 0.0001
LDL-cholesterol	*r*	0.27	0.38
	p	0.0004	< 0.0001
TG	*r*	0.60	0.34
	p	0.00001	< 0.0001
Total cholesterol / HDL	*r*	0.74	0.70
	p	< 0.00001	< 0.0001
CRP	*r*	0.69	0.73
	p	< 0.00001	< 0.0001
Fibrinogen	*r*	0.60	0.62
	p	< 0.00001	< 0.0001

Table IV. Correlation between Variables and Anti CP IgG Seropositivity for the CAD and Control Groups

Variables		CAD and Anti CP IgG seropositivity	Control cases and Anti CP IgG seropositivity
Total cholesterol	*r*	0.04	0.11
	p	0.66	0.38
HDL-cholesterol	*r*	− 0.82	− 0.79
	p	< 0.0001	< 0.0001
LDL-cholesterol	*r*	0.35	0.39
	p	< 0.0001	0.002
TG	*r*	0.61	0.57
	p	< 0.0001	< 0.0001
Total cholesterol / HDL	*r*	0.76	0.83
	p	< 0.0001	< 0.0001
CRP	*r*	0.71	0.74
	p	< 0.0001	< 0.0001
Fibrinogen	*r*	0.62	0.79
	p	< 0.0001	< 0.0001

disease. CP can multiply in macrophages and endothelial cells.[30-32] Immune complexes might be deposited on the vessel wall creating local inflammatory and procoagulant changes.[33] The host response to infectious agents usually involves a change in the process of hepatic protein synthesis. The cytokine interleukin 6 may mediate much of this switch from the production of housekeeping proteins such as albumin to greater synthesis of proteins collectively known as acute phase reactants, some of which may influence atherogenesis. Augmented production of

fibrinogen and plasminogen activator inhibitor during the acute phase response could promote thrombosis. Increased production of serum amyloid A protein can alter the potential function of HDL in cholesterol export from atheromatous lesions and in coronary risk. Also systemic infections can decrease HDL cholesterol concentrations.[34] In our study acute phase reactants like CRP and fibrinogen were found to be increased in CAD patients compared to control cases, and showed a direct correlation with the seropositivity for IgG antibodies to CP. In addition, we found increased TG, LDL levels and total cholesterol / HDL-cholesterol ratio in CAD, showing a positive correlation with anti CP IgG positivity for all cases, and low HDL-cholesterol levels in CAD, showing a negative correlation with the seropositivity for anti CP IgG for all cases. The mechanisms of these changes in cases with seropositivity for IgG antibodies to CP might be explained as above. Our patient group consisted of patients with chronic stable coronary heart disease and seropositivity for IgG antibodies to CP might be strongly due to the chronic persistent infection, as explained before by Mazzoli, *et al*,[35] Murray, *et al*,[36] and Laurila, *et al*,[28] who also found increased total cholesterol and decreased HDL-cholesterol levels in their coronary heart disease group, first showing a direct and second an inverse relation with the seropositivity for IgG antibodies to chlamydia pneumonia.[36] This was consistent with our findings, except for the total cholesterol levels. In our study the level of total cholesterol did not exhibit any difference between the two groups.

The most commonly reported infection induced lipid abnormalities in man and experimental animals have been decreased HDL-cholesterol and raised triglycerides and very low density lipoprotein.[37-39] These effects are part of the acute phase response and appear to be mediated by cytokines such as tumor necrosis factor, interleukin-1 and interleukin-6,[38] and have been observed in persons with serological evidence of CP infection.[28] The effect of infection on total and LDL-cholesterol is less clear. But it has been reported in humans and primates that total and LDL-cholesterol values decrease in severe bacterial infections.[37,39,40] These changes are seen in acute infections, but the lipid response to a chronic infection could be different from an acute one with some similarities like in our cases who showed decreased HDL-cholesterol levels and increased TG levels. The presence of normal but relatively high levels of CRP and fibrinogen in our patient group may be a nonspecific phenomenon reflecting cytokine mediated hepatic production triggered by most forms of inflammation, infection or tissue injury.

The results of the present study demonstrate that chronic or acute infection with chlamydia pneumonia may mediate the progression of atherosclerotic coronary heart disease by altering the blood lipid profile and increasing blood procoagulant activity.

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