

## STUDY OF CYTOMEGALOVIRUS ANTIBODY IN ATHEROSCLEROTIC PATIENTS IN TABRIZ

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### ABSTRACT

To evaluate the correlation of cytomegalovirus (CMV) and coronary artery disease (CAD), one-hundred patients with CAD and the same number of healthy individuals as a control group were randomly selected and studied for anti-CMV using ELISA method. Ninety percent of patients and 77 percent of the control group were anti-CMV positive and statistical analysis showed a significant correlation between these groups ( $p < 0.05$ ). Certain risk factors such as hypertension, hyperlipidemia, diabetes, smoking, type A personality and familial history were also studied. The distribution of these factors in the patient group were higher than those of the control group and a significant correlation was observed between these groups, but no dependency was observed between anti-CMV and the above parameters in the patient group. Results of this study showed a meaningful correlation between the anti-CMV level and coronary artery disease.

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### INTRODUCTION

Recent investigations have provided evidence that a member of the herpesvirus family can cause atherosclerosis in chickens. *In vitro* experiments suggested that a virus-induced alteration of cellular metabolism, which results in the accumulation of cholesterol and cholesteryl esters, may be the primary mechanism in the development of viral atherosclerosis.

Evidence supporting the involvement of one or more members of the herpesvirus family in human atherosclerosis is much more circumstantial. Cytomegalovirus (CMV) is prevalent, increasing with age, such that a majority of the human population becomes infected by adulthood.<sup>1,2</sup> The relationship with vascular smooth muscle cell proliferation in either atherosclerosis or post-angioplasty restenosis and

viral markers in arterial smooth muscle cells can be detected.<sup>1-3</sup> This prospective study was designed to assess the clinical significance of antibodies to cytomegalovirus in patients with risk factors involved in CAD.

### PATIENTS AND METHODS

From March 1994 to August 1995, 100 patients with coronary artery disease and 100 age and sex matched individuals without any evidence of coronary artery disease as a control group were randomly selected. All sera samples (cases and control groups) were serologically studied by ELISA method for anti-CMV and the major risk factors involved in CAD (diabetes, hyperlipidemia, and hypertension). Smoking habits, familial history, and type

## Correlation Between Anti-CMV Antibody Level and CAD

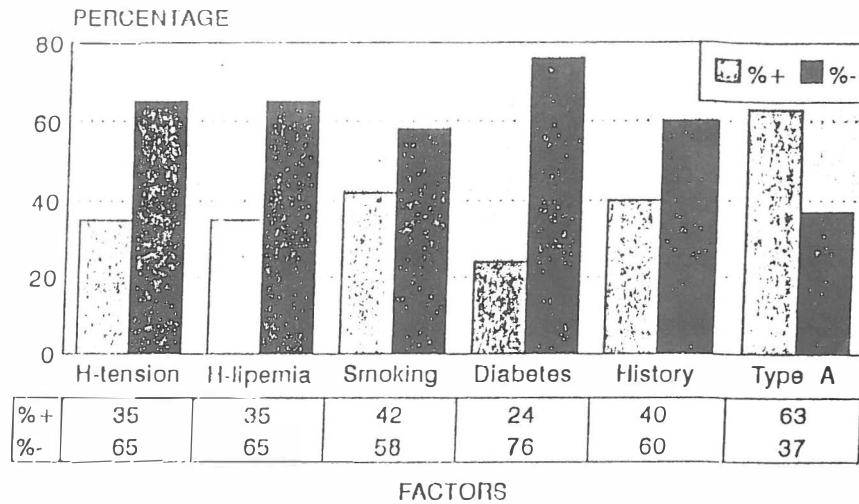


Fig. 1. Distribution of certain risk factors in CAD patients in regard to anti-CMV positivity.

Table I. Sex and age distribution in patient and control groups.

Group	Sex	n	%	Age (year)		X <sup>2</sup> ± SD
				Min	Max	
Patients	Male	80	80	35	75	52.6+9.9
	Female	20	20	42	62	51.5+5.8
Control	Male	79	79	35	75	52.5+10.9
	Female	21	21	40	65	50.9+8.4

Table II. Hypothesis of CMV initiation and development of atherosclerosis.

- 1- Systemic CMV infection.
- 2- Infection of arterial endothelium.
- 3- Polymorphonuclear leukocyte adherence (inflammatory response) leads to damage of endothelium.
- 4- Leakage of CMV from infected endothelial cells and exposure of neighboring smooth muscle cells within the arterial wall.
- 5- Latent and persistent infections of smooth muscle cells, detected by tracing viral genome or antigens.
- 6- CMV may transform cells and cause smooth muscle cells to proliferate locally, without destroying them, and may induce changes in cellular metabolites, including cholesterol accumulation.
- 7- At the site of CMV latency, the arterial lesion may be periodically activated (perhaps by hormones), followed by viral infection of the endothelial cells. This would result in bouts of adherence of PMN leukocytes and further proliferation of the surrounding smooth muscle cells.

A personality factors were also studied in the patient group. Comparison of results were made using the Chi-square and Fisher exact statistical tests.

### RESULTS

The present study is based on 100 atherosclerotic

patients and 100 sex and age matched healthy individuals as the control group. The number, sex and mean age of the patient and control groups are shown in Table I. The sex and age distribution of the patients is more or less similar to most previous investigations.

Ninety patients (90%) and 77 of the control group (77%) were anti-CMV positive. Statistical analysis showed a significant correlation between the patient and control groups ( $p=0.02$ ).

The distribution of the involved factors in regard to the anti-CMV conditions are shown in Fig. 1. Although in some cases, such as smoking, high titers of anti-CMV were noticed, statistical analysis nevertheless showed no significant correlation between these risk factors and the anti-CMV titer.

### DISCUSSION

Cytomegalovirus antigen has been initially shown by Peterie et al. in arterial smooth muscle cells of atherosclerotic patients, and then Capron et al. showed that CMV infection probably has a crucial role in increasing the severity of atherosclerotic damage.<sup>4,5</sup>

The role of CMV in the pathogenesis of the atherosclerosis process is presented in Table II.

Span et al. showed that herpesvirus infection increases

the adhesion of monocytes and polymorphonuclear (PMN) cells to arterial endothelial cells and this phenomenon results in cell damage and triggers the process of atherosclerosis.<sup>6</sup>

In seroepidemiologic studies, high levels of CMV antibodies were found to be associated with clinically manifest atherosclerotic disease, suggesting that a periodically activated latent infection or continuously active infection is present in patients with atherosclerosis. Since CMV DNA, but not infectious virus, is found in arterial cells, the arterial wall itself might be the site of latency.<sup>7</sup>

Adam et al. and Musiani et al. showed that the prevalence rate of anti-CMV titer in atherosclerotic patients who had undergone bypass surgery was higher than the control group.<sup>8,9</sup>

Nieto et al. showed that case subjects had higher mean CMV antibody titers in 1974 sera than control subjects.<sup>2</sup> Results of our study showed that anti-CMV antibody titers in the patient group were higher than that of controls, which corresponds with the findings of Melnick et al., Musiani et al., and Sorlie et al. These findings suggested a possible role and correlation of CMV in the induction and development of atherosclerosis in these patients.<sup>9-11</sup>

CMV infection is usually subclinical and increases with age, transfusion, organ transplantation and immunosuppression.<sup>12-14</sup> Many of these factors such as age and immunosuppression are present in CAD patients. To determine the role of these factors in CAD patients suffering from CMV infections, they were also studied and no meaningful correlation was noticed between these parameters and CMV positivity. Since many factors such as diabetes, hyperlipidemia, hypertension, smoking, etc. are involved in the formation, development, or process of atherosclerosis, and may affect the results of the study, these parameters and CAD was not observed. However, the high prevalence rate of anti-CMV titers in these patients indicates that there is a relationship between CMV and CAD. Detection of certain viral markers such as nucleic acid and antigens in arterial smooth muscle cells confirms this hypothesis.

Our findings indicate that CMV is probably involved in CAD, but further investigation is still required.

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