Seroprevalence of Antibodies to Microorganisms Known To Cause Arterial and Myocardial Damage in Patients with or without Coronary Stenosis

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Infections are assumed to play a role in coronary artery disease (CAD) and cardiomyopathies. Among microorganisms known to cause arterial and myocardial damage are Bartonella henselae, Borrelia burgdorferi, Chlamydia pneumoniae, Coxiella burnetii, Helicobacter pylori, human granulocytic Ehrlichia, Leptospira, Rickettsia conorii, and Treponema pallidum. Aims of the study were (i) to compare the seroprevalence of specific antibodies to microorganisms known to cause arterial and myocardial damage in patients with normal angiograms with regard to (a) possible causes of exertional dyspnea or anginal chest pain who underwent coronary angiography because of suspected CAD. Patients with normal angiograms (NA) were those in whom no more than 50% stenosis of any coronary artery was found. Patients with CAD were patients who underwent percutaneous transluminal coronary angioplasty. There were 50 patients with CAD (9 female) and 62 with NA (25 female), with a mean age of 62 years. All patients had antibodies to at least one microorganism: to B. henselae, 8% of CAD patients and 5% of NA patients; to B. burgdorferi IgG, 14% CAD and 6% NA; to B. burgdorferi IgM, 6% CAD and 3% NA; to C. pneumoniae lipopolysaccharide (LPS) IgA, 76% CAD and 77% NA; to C. pneumo-
niae LPS IgG, 80% CAD and 90% NA; to C. burnetii, 0% CAD and 5% NA; to H. pylori, 92% CAD and 68% NA; to human granulocytic Ehrlichia, 8% CAD and 3% NA; to Leptospira IgG, 4% CAD and 2% NA; to R. conorii, 10% in both groups; and to T. pallidum, 2% CAD and 0% NA. The seroprevalence of antibodies to microorganisms known to induce arterial and myocardial damage does not differ between patients with CAD and NA.

MATERIALS AND METHODS

Patients. The group of patients with normal angiograms consisted of consecutive patients in whom a coronary angiography had been performed because coronary heart disease was suspected by clinical findings (exertional dyspnea or anginal chest pain) and noninvasive tests (stress test, scintigraphy, and echocardiography) and no relevant (>50%) stenosis of any coronary artery had been found. Excluded were patients in whom a coronary angiography was performed prior to valve surgery or organ transplantation. The group of patients with coronary heart disease consisted of consecutive patients who underwent percutaneous transluminal coronary angioplasty (PTCA) of one or more coronary artery stenosis. The coronary angiographies and PTCA were performed at the 2nd Medical Department of the Krankenanstalt Rudolfstiftung. All patients of both groups were invited for a follow-up visit between April and July 1999. During this visit, patients with normal coronary angiograms underwent extensive investigations, including a medical history, physical examination, 12-lead electrocardiogram (ECG), transthoracic 2-D, M-mode and Doppler echocardiography, and blood tests (blood sedimentation rate, red and white blood cell counts, thrombocyte count, transferrin saturation, creatine kinase, γ-glutamyl-transpeptidase, calcium, potassium, thyroid stimulating hormone, and analysis of the hemochromatosis gene mutations C282Y and H63D). Based on these investigations, possible causes of dyspnea and anginal chest pain were assessed according to predefined criteria (Table 1) (17). Patients with coronary heart disease underwent clinical examination and exercise testing 3 months after PTCA. At this visit, blood was taken from both groups for serologic investigations comprising specific antibodies to the following microorganisms, which are known to cause arterial and myocardial damage: B. henselae, B. burgdorferi, C. pneumoniae, C. burnetii, H. pylori, human granulocytic Ehrlichia, Leptospira, R. conorii, and T. pallidum. The test systems used are listed on Table 2. All tests were performed according to the manufacturer’s instructions at one institute (Klinisches Institut für Hygiene der Universität Wien). Informed consent was obtained from all patients, and the study was approved by the institutional ethics committee.

RESULTS

Included in the study were 112 patients, 50 with coronary heart disease who underwent PTCA between January and
April 1999 and 62 with normal coronary angiograms performed between January and December 1998. The group with coronary heart disease consisted of 9 female and 41 male patients with a mean age of 62 years. In the group with normal coronary angiograms (25 female, 37 male, mean age of 62 years), the patients suffered from anginal chest pain (n = 38 [61%]), exertional dyspnea (n = 12 [19%]), or a combination of exertional dyspnea and anginal chest pain (n = 12 [19%]). In this group, all patients except one underwent one or more noninvasive tests prior to coronary angiography: echocardiography (n = 25), bicycle stress test (n = 3), echocardiography and bicycle stress test (n = 14), echocardiography and scintigraphy (n = 6), bicycle test and scintigraphy (n = 1), or echocardiography, bicycle test, and scintigraphy (n = 12). In patients with normal coronary angiograms, 47 patients had smooth normal vessels and 15 patients had coronary sclerosis but no significant (>50%) stenosis. In 48 of the 62 patients with normal coronary angiograms, one or more causes of cardiac symptoms could be assessed: arterial hypertension (n = 44), homoyzogous for HFE gene mutation (Cys 282→Tyr) or HFE gene mutation (His 63→Asp) or heterozygous for both mutations (7, 19), hypothyroidism (n = 6), hypoparathyroidism (n = 3), tachycardiomyopathy (n = 5), and neuromuscular disorder (n = 7). In the remaining 14 patients with normal coronary angiograms, the cause of exertional dyspnea and anginal chest pain remained unknown (Table 1) (17). The seroprevalence of antibodies known to cause arterial and myocardial damage is listed on Table 3. All included patients had antibodies to at least one microorganism. The seroprevalence was similarly distributed between patients with coronary artery stenosis and with normal coronary angiograms. Antibodies to <i>C. pneumoniae</i> and <i>H. pylori</i> were most prevalent in both groups.

**TABLE 1. Diagnostic criteria for possible causes of symptoms and their prevalence in group of patients with normal angiograms**

| Cause of symptoms                  | Diagnostic criteria                                                                 | Prevalence (n) |
|------------------------------------|-------------------------------------------------------------------------------------|----------------|
| Arterial hypertension              | History of arterial hypertension or treatment with antihypertensive drugs             | 44             |
| Haemochromatosis                   | Homozygous for HFE gene mutation (Cys 282→Tyr) or HFE gene mutation (His 63→Asp)   | 2              |
|                                    | or heterozygous for both mutations (7, 19)                                          |                |
| Hypothyroidism                     | Elevated TSH values (>4.0 μIE/ml)                                                  | 3              |
| Hypoparathyroidism                 | Decreased serum Ca (<2.1 mmol/liter) and parathormone values (12)                   | 0              |
| Tachycardiomyopathy                | Heart rate of >100/min at resting ECG and decreased systolic function (2)           | 5              |
| Amyloidosis                        | Biopsy of the involved tissue, showing amyloid deposition (21)                     | 0              |
| Neuromuscular disorder             | Evidence from medical history, clinical examination, biochemical data, and electromyogram of a myopathy or polyneuropathy (9) | 7              |
| Unknown                            | Absence of any of the above-mentioned abnormalities                                 | 14             |

An association of coronary heart disease and infections with <i>C. pneumoniae</i>, an important respiratory pathogen, has been initially found by seroepidemiologic studies (23). More recently, the presence of <i>C. pneumoniae</i> in atheromatous plaques has been shown (3). At present, controversial results are available about the role of <i>C. pneumoniae</i> in the development of coronary heart disease. Several authors found an association (18, 24) whereas others did not (5, 6). Another microorganism suspected to play a role in coronary atherosclerosis is <i>H. pylori</i>, the main etiologic factor in gastritis and peptic ulcer disease. <i>H. pylori</i> infection is postulated to have an effect on clotting mechanisms and lead to a prothrombotic state (10). Again, controversial results are available about the role of <i>H. pylori</i> in the development of coronary heart disease. Several authors found an association (20), whereas others did not (5, 10, 18), or found an association which can be adequately explained by the much stronger association of <i>H. pylori</i> infection with age and social class, both of which are linked with coronary heart disease (15). Nearly all our patients with coronary stenosis (92%) had antibodies to <i>H. pylori</i>, whereas in the group with normal coronary angiograms, they were found in only 68% of the patients. This finding may be due to the differing proportions of male patients in the group with coronary heart disease (82%) and with normal coronary angiograms (60%). Furthermore, epidemiologic studies show that the seroprevalence of antibodies to <i>H. pylori</i> is generally higher in men than women (15, 22). One reason for the controversial results about the association of infections with <i>C. pneumoniae</i>...
**TABLE 2. Test systems used in order to identify specific microorganisms known to cause arterial and myocardial damage in patients with coronary heart disease (5, 11, 18, 25, 26).**

| Pathogen Test System | Antigen Immunoglobulin |
|----------------------|------------------------|
| *Treponema pallidum* | Lipopolysaccharide (LPS) |
| *Borrelia burgdorferi* | LPS |
| *Chlamydia pneumoniae* | LPS |
| *Helicobacter pylori* | LPS |
| *Human granulocytic ehrlichiosis* | LPS |

**TABLE 3. Seroprevalence of antibodies to microorganisms known to cause arterial and myocardial damage in patients with coronary heart disease.**

| Microorganism | Antibodies | No. (%) of patients with specific antibodies |
|---------------|------------|-------------------------------------------|
| *Treponema pallidum* | IgG, IgM | 4 (7) |
| *Borrelia burgdorferi* | IgG, IgM | 5 (8) |
| *Chlamydia pneumoniae* | IgG | 4 (6) |
| *Helicobacter pylori* | IgG | 0 (0) |
| *Human granulocytic ehrlichiosis* | IgG | 1 (2) |

**TABLE 4. Diagnostic criteria for myocarditis.**

| Criteria | Definition |
|---------|------------|
| ECG     | Sustained ventricular tachycardia, ventricular arrhythmias, new left bundle branch block, or prolonged QT interval |
| Echocardiography | Left ventricular dilatation, wall thickening, regional wall motion abnormality |
| Cardiac MRI | Late gadolinium enhancement |
| Cardiac CT | Late enhancement |
| Cardiac catheterization | No obstructive coronary artery disease |
| Cardiac biopsy | Myocardial inflammation, fibrosis, or necrosis |

**TABLE 5. Correlation of seropositivity to microorganisms known to cause arterial and myocardial damage in patients with coronary heart disease.**

| Microorganism | IgG | IgM |
|---------------|-----|-----|
| *Treponema pallidum* | 2 (4) | 1 (2) |
| *Borrelia burgdorferi* | 7 (14) | 4 (6) |
| *Chlamydia pneumoniae* | 0 (0) | 3 (5) |

**TABLE 6. Correlation of seropositivity to microorganisms known to cause arterial and myocardial damage in patients with coronary heart disease.**

| Microorganism | IgG | IgM |
|---------------|-----|-----|
| *Treponema pallidum* | 2 (4) | 1 (2) |
| *Borrelia burgdorferi* | 7 (14) | 4 (6) |
| *Chlamydia pneumoniae* | 0 (0) | 3 (5) |
| Target microorganism(s) of antibody | Patient characteristics | Age/sex | Cause(s) | Echocardiogram result(s) |
|-----------------------------------|-------------------------|---------|----------|-------------------------|
| Helicobacter pylori and no other antibodies |                          | 36/M    | AH       | LVH                    |
|                                    |                          | 74/M    | AH       | DIL, SYD, LVH          |
|                                    |                          | 52/M    | AH, TM   | DIL, LVH, DIA          |
| Helicobacter pylori, Chlamydia pneumoniae LPS IgG |                          | 72/M    | AH       | Normal                 |
|                                    |                          | 68/F    | AH       | LVH, DIA, ILVAT        |
|                                    |                          | 60/F    | AH       | LVH                    |
|                                    |                          | 62/M    | AH       | DIL, LVH               |
|                                    |                          | 68/F    | AH       | DIL, LVH, DIA          |
|                                    |                          | 68/F    | AH, HY   | LVH, DIA               |
| Helicobacter pylori, Chlamydia pneumoniae LPS IgG, Chlamydia pneumoniae LPS IgA |                          | 59/M    | HY       | LVH, SYD               |
|                                    |                          | 72/F    | HC       | DIL, LVH, SYD          |
|                                    |                          | 62/F    | AH       | Normal                 |
|                                    |                          | 57/M    | AH       | LVH, DIA               |
|                                    |                          | 69/M    | AH       | Normal                 |
|                                    |                          | 72/F    | AH       | Normal                 |
|                                    |                          | 78/F    | AH       | LVH                    |
|                                    |                          | 47/M    | AH       | LVH, SYD               |
|                                    |                          | 54/F    | AH       | LVH, ILVAT             |
|                                    |                          | 69/F    | AH       | LVH, DIA               |
|                                    |                          | 60/M    | AH       | LVH, SYD               |
|                                    |                          | 79/M    | AH       | DIL, LVH, SYD          |
|                                    |                          | 57/M    | AH       | LVH                    |
|                                    |                          | 48/M    | AH, NM   | DIL, LVH, SYD, ILVAT   |
|                                    |                          | 55/M    | AH, TM   | DIL, LVH, SYD          |
|                                    |                          | 51/M    | AH, TM   | LVH, DIA               |
| Helicobacter pylori, Borrelia burgdorferi IgG, Rickettsia conorii, Chlamydia pneumoniae LPS IgG, Chlamydia pneumoniae LPS IgA |                          | 40/F    | AH       | LVH                    |
|                                    |                          | 65/F    | AH       | LVH, DIA               |
| Helicobacter pylori, Coxiella burnetti, Chlamydia pneumoniae LPS IgG |                          | 59/M    | AH       | LVH                    |
| Helicobacter pylori, Coxiella burnetti, Chlamydia pneumoniae LPS IgG, Chlamydia pneumoniae LPS IgA |                          | 53/M    | AH       | LVH, SYD               |
| Helicobacter pylori, Bartonella henselae, Rickettsia conorii |                          | 54/M    | AH       | LVH, DIA               |
| Chlamydia pneumoniae LPS IgG |                          | 74/F    | AH       | LVH, DIA               |
| Chlamydia pneumoniae LPS IgG, Chlamydia pneumoniae LPS IgA |                          | 55/M    | NM       | DIL, SYD, ILVAT        |
|                                    |                          | 73/F    | AH       | LVH, DIA               |
|                                    |                          | 64/F    | AH       | LVH, SYD, ILVAT        |
|                                    |                          | 59/F    | AH       | Normal                 |
|                                    |                          | 64/M    | AH       | LVH                    |
|                                    |                          | 74/M    | AH       | DIL, LVH, DIA          |
|                                    |                          | 70/F    | AH, HC   | DIA                    |
|                                    |                          | 54/M    | AH, NM   | DIL, LVH, DIA, ILVAT   |
|                                    |                          | 58/M    | AH, NM   | LVH, ILVAT             |
|                                    |                          | 30/M    | AH, NM   | LVH                    |
|                                    |                          | 45/M    | AH, TM   | LVH, DIA               |
|                                    |                          | 52/M    | AH, NM, TM | DIL, SYD, ILVAT |
| Rickettsia conorii, Chlamydia pneumoniae LPS IgG, Chlamydia pneumoniae LPS IgA |                          | 64/F    | AH       | LVH, DIA               |
|                                    |                          | 59/M    | AH, NM   | DIL, LVH, SYD, ILVAT   |
| Bartonella henselae, Chlamydia pneumoniae LPS IgG, Chlamydia pneumoniae LPS IgA |                          | 56/F    | AH, HY   | Normal                 |
| Leptospira IgG, Chlamydia pneumoniae LPS IgG |                          | 69/M    | AH       | LVH, SYD               |

*AH, arterial hypertension; DIA, diastolic dysfunction (E/A ratio of <1 or restrictive filling pattern); DIL, left ventricular enddiastolic diameter of >57 mm; HC, hemochromatosis; HY, hypothyroidism; ILVAT, isolated left ventricular abnormal trabeculation; LVH, left ventricular wall thickness of >11 mm; NM, neuromuscular disorder; SYD, left ventricular fractional shortening of <30%; TM, tachycardiomyopathy.
infection. Additionally, testing for other antibodies to microorganisms known to induce arterial damage, like cytomegalovirus, or myocardial damage, like viruses, other bacteria, fungi, and protozoa, has not been performed.

It is concluded that assessment of the seroprevalence of antibodies to microorganisms known to induce arterial and myocardial damage is not useful to clarify the etiology of exertional dyspnea or anginal chest pain in patients with normal coronary angiograms, since they are similarly distributed as in the general population and do not differ between patients with coronary artery stenosis and with normal coronary angiograms. These findings from a relatively small number of patients have to be confirmed in a larger study.

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