have been impractical to stratify patients according to each of the prognostic criteria; moreover, the groups were very similar.

One difference between the modified Glasgow eight-factor predictive system of severity that we used and the standard system[10] was the inclusion of age >55 years in the former. Our own data (unpublished), and those of others,[13-27] had shown that age, but not aminotransferase, was important in predicting outcome, and this finding was confirmed in the present study. It has been suggested that the favourable effect of ECRP/ES could be due to its beneficial effect on acute cholangitis rather than on acute pancreatitis.[28] The concomitant presence of acute cholangitis with acute pancreatitis is associated with a high incidence of pancreatic complications following ERCP ± ES.[29-31] When we excluded patients who presented with associated acute cholangitis from the analysis, ERCP/ES was still superior to conventional treatment, either for the overall groups ($p = 0{\cdot}02$) or only for those predicted to have severe attacks ($p = 0{\cdot}003$).

One criticism of our work was the small number of severe cases (12) with CBD stones in the ERCP/ES group.[28] Nevertheless this number represented 63% of those with confirmed stones who had successful ERCP. Furthermore, in a larger series patients in whom CBD stones persisted were those with the highest incidence of complications.[32] It is these patients therefore who are most likely to benefit from ES.

In conclusion, this study has shown that ERCP and ES are safe procedures in patients with acute pancreatitis, although a skilled endoscopist is required. Compared with conservative treatment morbidity was lower and hospital stay shorter with ERCP ± ES among patients with severe pancreatitis. We emphasise that the two procedures can be considered only as part (albeit an important part) of the overall management of these patients.

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SEROLOGICAL EVIDENCE OF AN ASSOCIATION OF A NOVEL CHLAMYDIA, TWAR, WITH CHRONIC CORONARY HEART DISEASE AND ACUTE MYOCARDIAL INFARCTION

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Summary Paired sera from 40 male patients with acute myocardial infarction (AMI), 30 male patients with chronic coronary heart disease (CCHD), and 41 controls, matched for sex, age, time, and locality were investigated for antibodies to a novel type of *Chlamydia* sp, TWAR, and to chlamydial lipopolysaccharide (LPS) group antigen. 27 patients with AMI (68%), and 15 (50%) patients with CCHD had raised IgG (⩾128) and/or IgA (⩾32) titres in the microimmunofluorescence test with chlamydia TWAR. Both frequencies were significantly higher than in the controls (7, 17%). 26 (68%) of 38 patients with AMI also showed a significant seroconversion in enzyme immunoassay with LPS antigen; this response was absent in all patients with CCHD and all but 1 of the controls. Chronic chlamydial infection could be a factor in the pathogenesis of cardiovascular diseases.

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Introduction

Chlamydia spp have been recognised as potential cardiovascular pathogens and implicated in various valvular heart diseases. There have been reports on myocarditis associated with *C trachomatis*[1,2] and *C psittaci*[3,4] infections; endocarditis has been demonstrated in infections caused by both species;[5,6] and major arterial emboli caused by *C psittaci* have been described.[7] In addition, an epidemiological association of primary myocardial disease and widespread chlamydial infection was indicated as early as 1967.[8,9] This observation was not pursued further because widespread epidemics could not be attributed to the rare *C psittaci*.

The discovery of a new *Chlamydia* sp, TWAR, has revolutionised our notion of respiratory chlamydial infections. *Chlamydia* TWAR has been implicated as a causative agent of several common respiratory infections, especially pneumonias.[10,11] Results of studies have shown it to be a new chlamydial species (proposed name *C pneumoniae*)[12,13] causing widespread epidemics in young adults in northern Europe. In Finland *Chlamydia* TWAR causes about 5–10% of pneumonia cases outside epidemics; in military recruits up to 30% of pneumonias arise in epidemics caused by this strain.[14,15]

We have investigated the association between antibody titres to *Chlamydia* TWAR, chronic coronary heart disease (CCHD), and acute myocardial infarction (AMI).

Subjects and Methods

Patients and Controls

Two groups of patients were investigated between Sept 15, 1983, and Feb 6, 1985, at Helsinki University Central Hospital. The AMI group consisted of 40 consecutive men (mean age 44·5 years, range 34–50) admitted because of an acute myocardial infarction. Inclusion criteria were: male gender, age 50 years or less, resident in Helsinki or immediate neighbourhood, onset of symptoms within 36 h before admission, and verification of AMI by typical changes in the electrocardiogram (ECG) and raised serum creatinine phosphokinase MB-isoenzyme activity. The CCHD group consisted of 30 consecutive men (mean age 41 years, range 28–50) admitted for coronary angiography because of severe chronic symptoms of angina pectoris. 19 had had AMI. Subjects with AMI within 6 months before admission were excluded. The patients lived in the same area as the AMI group and all had CCHD documented both clinically and angiographically.

The controls were a computer based random sample of 41 men from the official records of the city of Helsinki for the same area as the patients. 65% of those invited agreed to participate; no one refused because of an acute infection. The most common cause for refusal was lack of time. None of the controls had any signs or symptoms of coronary heart disease as judged by a negative history and a normal resting ECG. Apart from 1 man treated with a beta-blocking agent for hypertension, all subjects were free of chronic disease or treatments. The controls were selected to represent the same age range (mean 39·1 years, range 30–50) as the patients, and they were invited to attend successively within 1–3 weeks after the admission of an index case with AMI.

Serum samples for measurement of antibodies were taken on admission and 4 weeks later from all individuals, with the exception of 2 patients with AMI (1 died and 1 dropped out).

Micro-immunofluorescence (Micro-IF) Test

A modification of Wang and Grayston's[16] micro-IF assay was used to measure *Chlamydia* TWAR antibodies. The TWAR antigen (Washington Research Foundation, Seattle, USA) consisted of formolinised purified HeLa 229 grown elementary bodies of TWAR strain AR 39. Fluorescein-isothiocyanate labelled conjugates against human immunoglobulins (γ-chain-specific, Kallestad, Austin, USA; μ-chain-specific, Dakopatt, Denmark; α-chain-specific, Orion Diagnostica, Finland) were used with amidoschwartz as counterstain. The sera were titrated in two-fold dilutions starting from 1 in 8, and a titre of 1 in 32 or more was judged positive.[19]

Enzyme-immunoassay for Measurement of Antibodies against Chlamydial Lipopolysaccharide (LPS-EIA)

Details and validation of the method have been described elsewhere.[17] Briefly, the antigen was LPS from core-deficient mutant of enterobacteria (purified Re-LPS from *Salmonella minnesota*, Calbiochem, USA) shown to crossreact with chlamydial group antigen.[18] Alkaline phosphatase labelled conjugates against human IgG, IgM, and IgA were obtained from Orion Diagnostica (Espoo, Finland). Titres were expressed as highest dilutions giving an optical density value of 0·3.

Statistical Analysis

Sample proportions were compared by chi-square test with Yates' correction. When the minimum estimated expected value was under 5, Fisher's exact test was used. Geometric mean titre (GMT) comparisons were done with the Mann-Whitney U test.

Results

TWAR-IF Antibodies (Table)

The recommended positivity limits in the micro-IF test with TWAR antigen are 1 in 32 for IgG and 1 in 16 for IgM;[19] the positivity limit for IgA has not been established. Both patient groups had significantly more TWAR IgG antibodies than had the controls. The geometric mean TWAR IgG and TWAR IgA titres were also higher in both patient groups than in the control group. There were, in both groups, significantly more patients than controls with a TWAR IgG titre of 1 in 128 or more and a TWAR IgA titre of 1 in 32 or more. IgG titres (1 in 128 or over) are seen in fewer than 15% of Finnish healthy adults during non-epidemic periods (Saikku P, unpublished). IgM antibodies were not found. TWAR-IF antibody levels did not differ between the AMI and CCHD groups.

IgG OR IgA TITRES AGAINST CHLAMYDIA TWAR AND SEROCONVERSION IN IgM CLASS BETWEEN PAIRED SERA IN ENZYME IMMUNOASSAY (EIA) TEST WITH Re-LPS ANTIGEN IN PATIENT AND CONTROL GROUPS

—	AMI (n = 40)	CCHD (n = 30)	Control (n = 41)	AMI *vs* CCHD (p)	AMI *vs* control (p)	CCHD *vs* control (p)
TWAR IgG ⩾32 (no of patients)	34 *(85%)*	26 *(87%)*	25 *(61%)*	NS	0·02	0·017
TWAR IgG ⩾128 (no of patients)	20 *(50%)*	14 *(47%)*	6 *(15%)*	NS	0·0007	0·003
TWAR IgG GMT	78·79	78·79	30·42	NS	0·0002	0·0011
TWAR IgA ⩾32 (no of patients)	18 *(45%)*	11 *(37%)*	4 *(10%)*	NS	0·0004	0 0061
TWAR IgA GMT	20·39	17·96	10·67	NS	0·0008	0 0035
TWAR IgG ⩾128, IgA ⩾32 (no of patients)	27 *(68%)*	15 *(50%)*	7 *(17%)*	NS	0·00001	0·003
Re-LPS EIA ⩾3-fold increase in IgM class (no of patients)	26* *(68%)*	0	1	0·00001	0·00001	NS

NS = not significant (p > 0·05). GMT = geometric mean titre. *N = 38.

Antibodies to LPS Measured by EIA (Table)

Most patients did not have IgG or IgA antibodies against Re-LPS, and their IgM antibody levels were low (below 1 in 500) compared with those of the controls (1 in 500 to 1 in 2000, when present). However, nearly 70% of 38 patients with AMI for whom paired measurements were available showed a pronounced IgM antibody response to Re-LPS between the first and second serum samples taken four weeks apart. A response was also seen in IgG and IgA antibodies, but to a somewhat lesser extent than that in IgM antibodies. The antibody titres fell in the third serum sample (taken 3 months after AMI). None of the patients with CCHD and only 1 control showed seroconversion to Re-LPS in the paired serum samples.

Discussion

The micro-IF test with TWAR elementary bodies as antigen is a reliable method for measurement of species-specific antibodies to this serologically unique chlamydial species.[19,20] The target antigen is probably the main outer membrane protein of the organism. To avoid contamination with tissue lipids present in conventional chlamydial group antigen preparations produced from yolk sacs or cell cultures, we used Re-LPS antigen isolated from salmonella mutant bacteria in the EIA; this LPS is known to share a major carbohydrate epitope with chlamydial LPS.[18,21] We have shown earlier, with the same EIA method, that antibody responses to Re-LPS antigen are not found in non-chlamydial infections, including enterobacterial septicaemia and pyelonephritis (ref 17 and unpublished data). We have also tested paired sera from about 1200 patients with pneumonia for antibody responses to Re-LPS; the positive responses seen have been of chlamydial origin, as shown by micro-IF.[22] Thus we believe that the antibodies found in the present study, with the tests measuring antibodies to two different antigens, are associated with chlamydial infection.

In Finland, *Chlamydia* TWAR infections have arisen as widespread epidemics,[10] monitored most easily in military settings.[14,15] Because of these epidemics nearly half the adult male population in Finland has demonstrable IgG antibodies (titre 1 in 32 or more) against *Chlamydia* TWAR,[23] as is also found in other developed countries.[11] In the present study sera were collected just before a TWAR epidemic.[14,15] The findings in controls of low titre (1 in 32 or 1 in 64) antibodies against this chlamydia and only a few raised IgG (1 in 128 or more) or IgA (1 in 32 or more) antibody titre is in accordance with the antibody status between epidemics. However, the percentages of patients with CCHD or AMI who had IgG titres of 1 in 32 or over or 1 in 128 or over and the mean titre values were higher than those of the controls. Our chlamydia antibody findings did not correlate with other risk factors for AMI such as smoking, hypertension, serum lipid indices, and influenza-like illness preceding AMI (data not shown).

All chlamydial species have a tendency to cause chronic infections,[24,25] and recurrence of the disease is frequent despite treatment with antibiotics. Primary TWAR infections are characterised by a predominant IgM response, delayed IgG response, and a weak or absent IgA response in the micro-IF test, whereas secondary infections are characterised by an absence of IgM response, and prompt IgG and IgA responses (refs 11, 19, 26, 27, and Ekman MR, unpublished). Our patients had high, stable IgG and IgA titres without seroconversion and no IgM antibodies in the micro-IF test. Thus the antibody findings suggest a chronic *Chlamydia* TWAR infection in both the CCHD and AMI groups. The seroconversions in Re-LPS EIA seen in AMI group suggest that some AMI cases might be associated with an acute exacerbation of a chronic chlamydial disease. These seroconversions were seen predominantly in IgM class antibodies, evidently because of the carbohydrate nature of the crossreacting epitope.[18,21]

Our controls and patients were matched for time, age group, social status, and geographical area. Thus the possibility that exposure to the TWAR agent would have been different in the patients and controls is extremely small, suggesting that the differences in results between patients and controls are true. *Chlamydia* TWAR was identified only a few years ago and thus its epidemiology and annual changes in occurrence are poorly known in Finland and elsewhere. However, it would be of great interest to compare the epidemiology of *Chlamydia* TWAR and the frequency of AMI in Finland in the longterm.

The possible relation between chronic chlamydial infection and AMI and CCHD does not undermine the importance of established risk factors such as smoking and hypercholesterolaemia, but should be taken into consideration in studies of possible pathogenic mechanisms and the epidemiology of coronary heart disease.

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LOCALISATION OF 11β-HYDROXYSTEROID DEHYDROGENASE—TISSUE SPECIFIC PROTECTOR OF THE MINERALOCORTICOID RECEPTOR

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Summary In vitro the mineralocorticoid receptor is non-specific and does not distinguish between aldosterone and cortisol. In vivo certain tissues with this receptor are aldosterone selective (eg, kidney and parotid) whereas others with the same receptor are not (eg, hippocampus and heart). Experiments in rats showed that 11β-hydroxysteroid dehydrogenase (which converts cortisol to cortisone in man and corticosterone to 11-dehydrocorticosterone in the rat) was much more highly concentrated in aldosterone-selective tissues than in non-selective tissues. The localisation in the selective tissues was such that the enzyme could act as a paracrine or possibly an autocrine mechanism protecting the receptor from exposure to corticosterone. Autoradiographic studies showed that protection is lost when the enzyme is inhibited; ^{3}H-corticosterone and ^{3}H-aldosterone were bound to similar sites. These findings seem to explain why sodium retention, hypokalaemia, and hypertension develop in subjects with congenital deficiency of 11β-OHSD and those in whom the enzyme has been inhibited by liquorice.

Introduction

IN-VITRO experiments with the mineralocorticoid (type 1) receptor, either cytosolic preparations or cloned receptor expressed in transfected cells, have shown that its affinity is similar for aldosterone, cortisol, corticosterone, and deoxycorticosterone.[1-3] In vivo, by contrast, these type 1 receptors in the kidney, parotid, and colon are aldosterone-selective, though those in the hippocampus do not distinguish between aldosterone and corticosterone.[1,2] These results led Funder[4] to suggest that there must be a factor other than the receptor responsible for determining the aldosterone tissue specificity. He suggested that this might be extravascular corticosteroid binding globulin (CBG) which preferentially bound cortisol or corticosterone

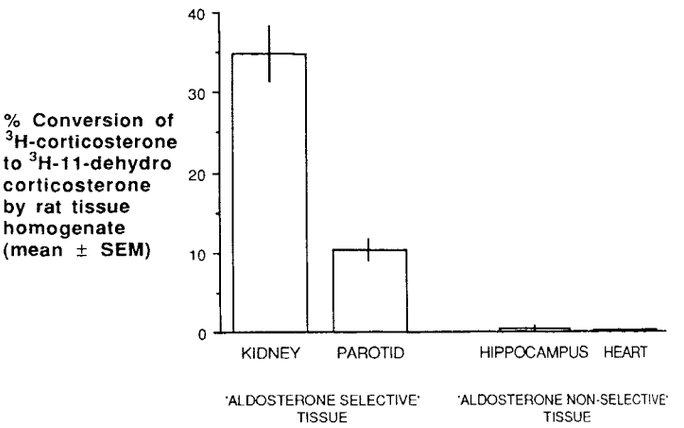

Fig 1—11β-OHSD activity in homogenates of rat renal cortex, parotid, hippocampus, and heart (n = 5).

(the major glucocorticoid in the rat). However, in the 10-day-old rat, which has very low levels of CBG, the in-vivo specificity of aldosterone was maintained despite the much higher levels of corticosterone.[5]

11β-hydroxysteroid dehydrogenase (11β-OHSD) is the microsomal enzyme complex responsible for the interconversion of cortisol and cortisone. It consists of two separate enzymes, one converting cortisol to cortisone (11β-dehydrogenase) and the other cortisone to cortisol (11-oxo-reductase).[6] Congenital deficiency of 11β-OHSD, originally described by Ulick,[7] is associated with severe hypertension, hypokalaemia, and suppression of plasma aldosterone and plasma renin activity—the syndrome of apparent mineralocorticoid excess. Our studies in an adult with this syndrome suggested that cortisol was acting as a mineralocorticoid.[8,9] The findings were in keeping with other results in Ulick's index case.[10] We hypothesised that the normal kidney used 11β-OHSD to convert cortisol to the inactive steroid cortisone and was thus protected from this effect. If this was so, then inhibition of 11β-OHSD would cause this protective mechanism to fail and allow access of cortisol to the non-specific renal mineralocorticoid receptors, resulting in sodium retention. We then found that the active component of liquorice (glycyrrhetinic acid) was a potent inhibitor of 11β-OHSD and proposed that this was the explanation for the sodium retaining and potassium losing actions of liquorice.[11] This answered the question why liquorice did not have these effects in severe adrenocortical insufficiency or after bilateral adrenalectomy.[11]

11β-OHSD is present in liver, kidney, gonads, placenta, lung, and intestinal mucosa.[12] The purification of 11β-OHSD has allowed the production of a specific antiserum

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