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Chronic Infection with Chlamydia Pneumoniae in COPD and Lung Cancer

AKADEMISK AVHANDLING

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Abstract

Lung cancer and chronic obstructive pulmonary disease (COPD) are major causes of morbidity and mortality throughout the world. Smoking is the main cause for both diseases, but other factors seem to contribute. *Chlamydia pneumoniae* (Cpn) is an obligate intracellular bacterium with a unique biphasic replicative cycle associated with respiratory infections. The ability to cause chronic infections is characteristic for bacteria of the family *Chlamydiaceae*. Persistent elevated IgA antibodies to Cpn is used as a marker for chronic Cpn infection. The aims of the thesis were to study the prevalence of chronic Cpn infection in patients with lung cancer (I), to study the prevalence of chronic Cpn infection in relation to lung function in patients without lung cancer (II), to study a new treatment regimen in patients with longstanding airway and/or pharyngeal symptoms and chronic Cpn infection (III), and to detect Cpn in cytospin preparations from bronchoalveolar lavage (BAL) fluid and in lung tissue from patients with COPD (IV). In studies I-II we investigated patients who underwent bronchoscopy due to longstanding airway symptoms and/or pathological chest X-rays.

Study I: 128 men and 70 women with lung cancer (LC) were included. Currently smoking or ex-smoking consecutively collected blood donors and 70-year olds from a population study were used as control groups. Blood specimens for specific Cpn antibodies were analysed using the microimmunofluorescence (MIF) technique. The prevalence of Cpn IgG antibody titres of $\geq 1/512$ was 57% in male LC patients compared to 27% in male 70 year olds and 17% in male blood donors. The prevalence of Cpn IgA antibody titres $\geq 1/64$ was 69% for male LC patients compared to 25% and 20% for respective control groups. The difference between male patients and controls was statistically significant. For female LC patients a statistically significant difference was found in prevalence only regarding IgA antibodies; 57% compared to 30% and 9% for the control groups.

Study II: 199 patients for whom spirometry and paired serum samples were available were included. Thirty patients fulfilled criteria for COPD. Antibodies in acute and convalescent sera were analysed by MIF. Chronic Cpn infection (defined as stable IgA titre $\geq 1/64$) was present in 85 patients. IgA titres increased with age in both COPD and non-COPD patients, but were higher in the COPD group independent of age. Chronic infection was associated with smoking and higher age, but no difference was observed between genders. A statistically significant association was observed between chronic Cpn infection and COPD. This remained after correction for smoking.

Study III: 103 patients were treated with azithromycin 500 mg daily for five days, repeated 3 times with a 23 days interval, or placebo. Patients were examined 4 months and one year after completed treatment. A general improvement of symptoms and less hawking was found in patients treated with azithromycin compared to placebo after 4 months, but there was no sustained difference one year after completed treatment. The antibody titres remained stable, and there was no influence on lung function.

Study IV: Cytospin preparations of BAL fluid from 14 COPD patients, 10 healthy smokers and 7 non-smokers were studied using a direct immunofluorescence technique for detection of Cpn. Lung tissue from 24 patients with emphysema were tested using immunohistochemistry (IHC) for Cpn. Serum samples were available for all patients except one undergoing BAL and in 11 of the emphysema patients. Elementary body like structures were detected in cytospin slides from 29% of COPD patients, 10% of healthy smokers and 14% of non-smokers. Cpn was detected in lung tissue from 8% of patients with advanced emphysema. COPD patients demonstrated a tendency to have specific Cpn IgA $\geq 1/64$ to a larger extent than the control groups, but no correlation was found between detection of Cpn and antibody titres.

Conclusions: An association was found between serological signs of chronic Cpn infection and COPD and lung cancer. Cpn was detected in the respiratory tract in a minority of the patients, but there was no correlation between the presence of organisms and antibodies. Azithromycin treatment resulted in transient effect on symptoms, without affecting the antibody titres or lung function.

Keywords: Chlamydia pneumoniae, chronic infection, lung cancer, COPD, treatment, detection

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