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The Role of Chlamydophila (Chlamydia) Pneumoniae in the Pathogenesis of Coronary Artery Disease

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1. Introduction

Atherosclerosis is a leading cause of death and disability in the modern world. Generations of researchers have worked to establish the risk factors of this disease. It was Rudolf Virchow who identified inflammation as one of those risk factors in his fundamental dissertation entitled Cellular Pathology, which was published in 1858. From this time onwards more that 250 risk factors of atherosclerosis have been found. Atherosclerosis is chronic progressive disease. Inflammation, similarly to atherosclerosis, activates endothelial cell damage, leucocyte migration and monocytes activation or smooth muscle proliferation. The discovery made at the end of the 20th century concerning the role that infection with Helicobacter pylori in the pathogenesis of peptic ulcer disease, has drawn much attention. Interest has been focused on the potential role of this and indeed other bacteria in pathogenesis of various chronic diseases. Epidemiological studies have revealed that the risk of such an infection increases in tandem with the age of the studied population (Veldhuyzen van Zanten et al., 1994). The role that Helicobacter pylori as well as other bacteria and viruses play in the pathogenesis of atherosclerosis was extensively studied at the end of the previous century in the nineteen nineties. These studies concluded that the connection between infection and atherosclerosis is much stronger for Chlamydophila pneumoniae (C. pneumoniae) than for Helicobacter pylori or any other organism (Blasi et al., 1996, Wald et al., 1997). A large numbers of studies reported on association between C. pneumoniae and symptoms of atherosclerosis such as coronary artery disease (Saikku et al., 1988. Jackson et al., 1997), carotid artery stenosis (Cochrane et al., 2003), lower extremities artery obstruction (Kuo et al., 1997) or aneurysms (Blasi et al., 1996. Lindholt et al., 1998)

2. History and taxonomy

Chlamydophila pneumoniae is a Gram-negative, obligate intracellular, bacterium that infects humans as a respiratory pathogen. This bacterium is responsible for many of cases of mild pneumonia, bronchitis and sinusitis in all parts of the world (Kuo et al., 1995). It was first named Chlamydia TWAR (for Taiwan Acute Respiratory), when close resemblance was found between bacteria isolated in patients from Taiwan and those

treated for acute respiratory failure in the USA (Grayston et al., 1986). The new strain was later found to be significantly different from the already known Chlamydia trachomatis and Chlamydia pisttaci, and was named Chlamydia pneumoniae (Grayston et al., 1989). The name was later officially changed to the one used at present, namely Chlamydophila pneumoniae.

3. Developmental cycle

C. Pneumoniae has a biphasic life cycle, existing as either an EB (elementary body) or a RB (reticulate body). The EB is the extracellular infectious non-replicating form which, when internalized by a susceptible cell in the human respiratory tract, differentiates into the metabolically active RB. The RB replicates thus forming an intracellular microcolony and then re-differentiates back into EB forms, which are released from the infected cell to begin next infection cycle. Although this explains why it can be found in the lungs it was nonetheless a surprise to discover that it can also be found in atherosclerotic vessels (Blasi et al., 1996). This fact had to be confirmed by means of the polymerase chain reaction method (PCR). Despite the fact that bacteria specific DNA was found in the diseased arteries no trace of the RNA was seen at the same time (Valassima et al., 2001). This suggests that what may be found in the arteries is not a metabolically active organism. The authors of this study conclude that the DNA remains only as a result of macrophages migration. But others have proved that in vitro C. pneumoniae can infect vascular endothelial cells, initiating lesion formation (Selzman et al., 2003). Animals infected with C. pneumoniae develop atherosclerosis lesion in arteries and several studies in man suggested an association between persistent infection and ischaemic heart disease.

4. Diagnosis of the C. pneumoniae infection

Culturing of the organism is the gold standard in the diagnosis of the infection, but sensitivity of this technique in the C. pneumoniae infection is only 60%. Compared the sensitivity of serological examination is close to 100%. This makes it most common method of diagnosing C. pneumoniae is to examine patient's serum for species-specific IgM, IgG and IgA class antibodies. Determining the dynamics of appearance and disappearance of particular immunoglobulin classes allows one to diagnose what kind of infections the patient suffers from: primary, chronic, or reinfection. In an acute primary infection, IgM class antibodies appear first and their levels remain increased for about 2 months, to gradually subside later. Next, the IgG class antibody titer levels increase, and then the same elevation is noticed in the IgA class. In case of successful treatment and no reinfection, the antibody levels slowly decrease, despite the fact that elevation in IgG class antibody levels is usually observed proportionally to the patient's age. Increased, but remaining stable, the level of IgG class antibodies, and, in particular, IgA class antibodies may indicate a chronic infection and/or frequently reoccurring infections. Persistent production of IgA class antibodies compared to long-lasting IgG antibodies, seems to be a good marker of chronic infection (Saikku et al 1999). C. pneumoniae primary infection is more common in children et persons at middle age. Approximately 50% of young adults have serological evidence of previous C. pneumoniae infection. Reinfection or persistent infection is more common in elderly persons and evidence of past infection have 75% of them. This disease is reported

more common in males (60-90%) that in females. The evidence of previous C. pneumoniae infection is higher in smokers end ex-smokers. The higher prevalence of smoking in men does not explain the C. pneumoniae antibody prevalence in men compared with women (Karvonen et al. 1994). After controlling for the effect of smoking, the risk of C. pneumoniae seropositivity remained 1.4 times higher in men than in women. In men, the estimated risk for C. pneumoniae seropositivity was significant only for smokers (1.5) and (1.7) for ex-smokers. C pneumoniae infection is more common in smokers. Smoking predisposes for the development of a chronic C pneumoniae infection. The synergistic negative effect of smoking and C pneumoniae chronic infection may be one mechanism in the pathogenesis of airway obstruction and atherosclerosis progression (von Hertzen et al., 1996).

5. Coronary artery diseases et C. pneumonia infection

C. pneumoniae usually causes acute upper respiratory tract infections, which range in severity from asymptomatic disease to severe pneumonia. It has been estimated to account for up to 20% of community-acquired pneumonia and, because it can maintain a chronic or latent infection, recurrence of the disease is frequent, despite treatment with antibiotics (Ewing et al., 2003). Such infections most frequently occur in elderly male smokers and such patients are naturally predisposed to atherosclerosis. However, there are other features to these infections, such as for example the periodical occurrence of epidemics every four years does not to seem to have much in common with atherosclerosis. Saikku was the first man to show that coronary artery diseases were more likely to have detectable in patients with higher anti - C. pneumoniae antibodies (Saikku et al., 1988). The conclusion reached was to start trials with antibiotics in such patients (Gurfinkel et al., 1997, 1999, Gupta et al., 1997, Muhlestein et al., 1998, Anderson et al., 1999, Grayston et al., 1999). Gurfinkel's group tested roxitromycin in patients with acute coronary syndromes. Gupta's group used azithromycin in patients with stable angina. A significant reduction in incidences of combined events including the recurrence of angina, myocardial infarction and death was noted in the early phase of the ROXIS trial (Gurfinkel et al., 1997). The following studies in the same patients did not show any long-term benefits of such therapy (Gurfinkel et al., 1999). Other groups have not been found to benefit from the use of antibiotics for the treatment of chronic or unstable angina (Zahn et al., 2003, O'Connor et al., 2005, Cannon et al., 2005). Indeed any evidence gathered from many trials performed to date does not demonstrate an overall benefit of antibiotic therapy in reducing mortality or cardiovascular events in patients with coronary artery disease (Andraws et al., 2005). The authors of the paper believe that the treatment with antichlamydial antibiotics failed to improve the clinical outcomes of acute coronary events and chronic disorders. One must accept that the problem is a difficult case to study. For example although the presence of C. pneumoniae in the arterial wall may be confirmed by laboratory tests such as PCR or IHC testing, a positive culture from such a specimen should not be expected. Published studies have detected C. pneumoniae in atherosclerosis arterial tissue using two different techniques such as polymerase chain reaction (PSR) and immunohistochemistry (IHC) but results are often difficult to interpret. (Cambell et al., 1995, Davidson et al., 1998) None of these techniques nowadays is perfect to detect the C. pneumoniae infection. There are long terms studies needed if we want to determine a potential role of C. Pneumoniae infection in the start of atherosclerosis plaque

or only in arteriosclerosis progression Coronary artery disease being a specific form of atherosclerosis, is a very difficult case for studying. Despite technical progress of visualisation of coronary artery, currently there are no examinations giving a possibility of observation in progressing of the atherosclerosis in these arteries. Diagnosis stated on classical coronarography do not give any information about the coexistence of coronary artery disease et chronic infection caused by C. Pneumoniae. In this situation we have not data on the infection anticipates in coronary artery. On the base of observation we know that laboratory inducted infection may lead to lowering of the HDL level and the increasing CRP if this examination at company high cholesterol diet. (Birck et al., 2011). Many states of the disease make this comparison difficult because in absolutely divergences illness early study od changes in artery or acute coronary syndrome and end stage circulatory insufficiency cause by coronary disease. Multiple sampling from the coronary artery is in practice impossible. That is why most researchers take species from the aortic wall. (Brykczyński 2000, Kribis et al., 2005). Frequently cited work of Kuo saying about C. Pneumonia founded directly in coronary artery wall was based only on 36 autopsies hearts (Kuo et al., 1993). In this paper the presents of C. Pneumoniae was confirmed during DNE study in 13 cases and 15 during immunochemistry examination. In total positive results was achieved in 20 cased. This says that positives results are not gained by different methods in all cases. The big advantage of this work is a confirmation of the presence of the metabolically active EB form of C. Pneumonia. Muhlestein presented positive results examining specimen of atherosclerotic plaque taking during coronary artery ednarteriectomy in immunochemistry examination in 73% of cases (Muhlestein et al., 1995). In many papers in diagnoses it is accepted to take into account the positive results in PCR and negative IHC or the other way round. It happens that positive results in patients without antibodies against C. pneumoniae take place. Researchers have always debated issues concerning the changing titers of antibodies against C. pneumoniae. It goes without saying that it is very important which antibodies are taken into account. It seems that the presence of IgA class antibodies is more important to diagnose a chronic C. pneumoniae infection than the more commonly present IgG antibody. The association between high titers of IgA antibodies and the subsequent risk of death from coronary artery disease was noted by Caerphilly prospective study (Strachan et al., 1999). Interestingly he did not show any relation between IgG antibodies and mortality. Lidholt described the presence of anti- C. pneumoniae IgA in patients with chronic abdominal aortic aneurysm (Lindholt et al., 1999). Others note the association between high titers of anti- C. pneumoniae IgA with the levels of fibrinogen and C-reactive protein (Toss et al., 1999, Zairis et al., 2003). It is interesting to note that although Saikku (1988) analyzed both IgA and IgG class antibodies, the other groups following him in this field limited their interest to only the IgG isotype (Zahn et al., 2003, O'Connor et al., 2005, Cannon et al., 2005). In my own research I have demonstrated the presence of antibodies against C. pneumoniae in 150 patients accepted for coronary surgery (Brykczynski 2001). Patients with coronary artery disease confirmed angiographic and qualified for coronary artery bypass grafting were enrolled. This study showed specific antibodies against C. pneumoniae in IgG class in 110 patients, and in IgA class in 90 patients. In 81 patients antibodies in both IgA class and IgG class were found. In 36 surgery patients no antibodies in either of those classes were found. Group consisting of 50 patients with high levels of antibodies against C. pneumoniae qualified for heart surgery and treated with antibiotic

(Rulid 2 x 150 mg) for 30 days prior to surgery. A monthly treatment with roxytromycin before the operation in those patients resulted in bringing down their levels of: fibrinogen, von Willebrand factor, complement component 3, prealbumin, acid α1-glycoprotein, homocysteine as well as total cholesterol levels. However the negative effect of this therapy was a fall in the level of HDL cholesterol. Other studies with azithromycin resulted in a similar reduction of inflammatory markers (Gupta et al., 1997, Anderson et al., 1999, Grayston et al., 1999). Despite the fact that these results may be encouraging it is nevertheless doubtful if one could base the diagnosis of infection only on the grounds of increased levels of antibodies. Furthermore no one has as yet described the result of antimicrobial treatment over a long time span. It may well be the case that any promising short-term result may not be necessarily related to the specific treatment of the C. pneumoniae infection. The beneficial influence of antibiotics on mortality observed in the Roxis trial was very limited. The lack of any clear results may be due to the fact that no established criteria of C. pneumoniae infection were given. The study was based on a single test of antibody titers, which may well only be a sign of a past but not necessarily an ongoing infection. Although all these doubts call for further research there exist very few studies in this area. It is for this reason that I have decided to follow my own patients, in which an examination of the presence of antibodies and the evaluation of the progress of coronary disease were performed 6 years after the operation (Brykczynski et al., 2010). The data were completed for all 150 patients in the first study 6 years after 82,5% patients were still alive, 17,4% patients died, and 6.45% living patients did not consent to participate in the control study. The objective of this study was 118 patients. The group consisted of 20% women, mean age 61.7 years, and 80% men, mean age 56.4 years In this study we also tried to evaluate the influence of C. pneumoniae infection on the late results of surgical treatment of coronary artery disease. In the first study IgA and IgG class antibodies were found in 53,4% patients, but in the control 83,9% patients had those antibodies. The number of patients with IgA class antibodies increased from 58,5% to 86,4% patients. In 30,5% patient's antibodies were found for the first time, and in 51,7% patients an significant increase of their titer occurred. Similarly, the number of patients with a positive test result for IgG class antibodies increased from 72.0% to 94,1% patients. In 22% patients IgG class antibodies were found for the first time, while in 39,8% patients an increase of their titer occurred. Only in 3,4% patients were no antibodies in either IgA or IgG class found – compared to 22,9% patients from the first study. Their preoperative coronary complaints were evaluated according to the Canadian Cardiovascular Score (CCS) scale. The average degree on the CCS score before operation was 3,8. Six years after the average CCS degree decreases to 1,65. These results show no connection between the increased serological symptoms of chronic infection caused by C. pneumoniae and coronary complaints. A steady increase of antibodies titers with the rise in the age of patients was observed. However this increase did not correspond with the intensity of the coronary artery disease symptoms. Many authors describe the link between the C. pneumoniae infection and pathogenesis of aortic aneurysms or with the progression of the atherosclerotic plaque in carotid arteries. Despite there being many published articles concerning this matter there remained to be found a universally accepted explanation of such an influence. Nonetheless a few hypotheses are proposed. One is the hypothesis which assumes that the C. pneumoniae infection spreads through the monocytes which get into the bloodstream via the lungs and then infiltrate the arterial walls as foam cells forming fatty streaks. The second theory is the plasma theory,

which explains the role of C. pneumoniae infection by its influence on the increasing plasma concentration of other independent factors related to atherosclerosis progression like fibrinogen, von Willebrand factor or C-reactive protein. Third theory links this infection with an autoimmunological reaction. At present the most popular theory is the one that assumes a crossover reaction with the heat shock proteins (HSP). C. pneumoniae contains heat shock protein like HSP 10, HSP 60 and HSP 70. All three of them can be found in the membrane complexes EB and RB. The human and bacterial proteins of this kind are very much alike. The expression of such proteins rises under stress, with high blood pressure or during infection. C. pneumoniae may produce large quantities of HSP. Another way may base on the synergistic negative effect of linked with advanced age, male sex, smoking habit, or higher level of fibrinogen et CRP. All of them are characteristic for chronic C. pneumoniae infection et atherosclerosis progression. Most researchers have been discouraged by lack of any clear proof that the C. pneumoniae infection is important in the pathogenesis of atherosclerosis. The fact that there is a multitude of independent risk factors predisposing to atherosclerosis may be changing due to the infection. This is because it makes it possible that a large number of these influences may not always be present in some patients, while in others may only be important In the presence of very specific circumstances. Without prospective studies based on large populations we may never learn whether the C. pneumoniae infection is an important risk factor for coronary artery disease or only an "innocent bystander " as suggested by West in his commentary (West, 1999). Patients with coronary artery disease represent a heterogeneous group, the same applies to patients with C. pneumoniae infections. Antibiotic treatment in acute or chronic infection may produce different results. One large study analyses the results of such treatment in atypical pulmonary infections (Arnold et al., 2007). These infections were caused by Legionella pneumophila, Mycoplasma pneumoniae and C. pneumoniae. The incidence of such infections is as high as 22% in the USA and 28% in Europe. In South America, Africa and Asia it is much lower. The diagnosis of pneumonia caused by the C. pneumoniae was arrived at in this study on the very strict basis with high IgG titer (1:512). Most of the patients were male and their mean age was over 65 years. The study retrospectively compares the group of patients treated with antibiotics covering the atypical infections with the group of patients who did not receive such treatment. Patients in the second group spend more time in hospital and had a higher mortality. Mortality in the second group was more than 10%. Perhaps this may be the explanation why there was a good short-term result of using antibiotics in the ROXIS study population of patients who had been treated for acute coronary syndromes.

6. Summary

In conclusion we have to state categorically that a high level of anti- C. pneumoniae antibodies is present in the majority of patients with diagnosed coronary artery disease. It seems that we may need to depend more on the IgA class antibodies examination in any future research because the IgG class antibodies are almost universally present in the population.

Additionally we need to establish a strict criteria to differentiate the acute and the latent C. pneumoniae infection. We still do not know what effect a C. pneumoniae infection has on the progression of coronary artery disease. Certainly a rise in the levels of the fibrinogen or

the CRP during such infections is a sign that it may have some kind of influence. This suggests that an atypical pneumonia caused by C. pneumoniae in patients with the coronary artery disease is not so "innocent".

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[1] PS. Preparing this publication I found very sad information that Dr Enrique Gurfinkel (ROXIS study) died of lung cancer 2 May 2011. www.theheart.org/article/1219603

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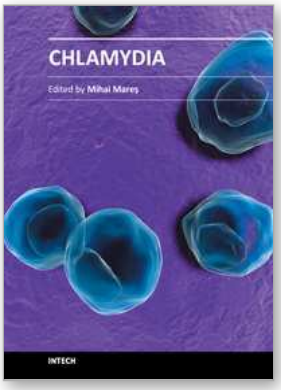

Chlamydia

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Nowadays, Chlamydia still represents a redoubtable pathogen. Among its consequences, the blindness in children and severe impairment of reproductive health in adults are the most mutilating. Worldwide, it is estimated that six million of people suffer from post-trachoma blindness and almost 90 million become sexually infected each year. Due to its silent evolution and sexually transmission, the chlamydial infection can occur in anyone. The book “Chlamydia - A Multifaceted Pathogen” contains an updated review of all-important issues concerning the chlamydial infection. It comprises 18 chapters grouped in four major parts dealing with etiology and pathogenicity, clinical aspects, diagnosis and prevention. The new molecular data about the pathogenicity and the exhaustive presentation of clinical findings bring novelty to the book and improve our knowledge about Chlamydia induced diseases.

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