Journal of Health Study and Medicine
2020, No. 4
pp. 115-133
DOI 10.36145/JHSM2020.30

Atherosclerosis and Chlamydia Pneumoniae: What Is the Connection?

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Introduction

Diseases resulting from unhealthy lifestyle are a growing global problem nowadays. The number of patients suffering from them is increasing at a different pace around the world [1]. One of these groups are cardiovascular diseases (CVD), which are the first cause of death in the European Union, despite the significant decrease in the associated standardised death rate in recent years [2]. Moreover, according to GUS (Główny Urząd Statystyczny) data, in 2014 CVD were the cause of 46% of all deaths in Poland [3]. However, if the patient's risk factors are identified in a timely manner and preventive measures are taken, the occurrence of CVD and other complications can be significantly averted [4].

The group of cardiovascular diseases include atherosclerosis, which is a chronic vascular disease [5]. The process can start very early, and the first changes in the form of rolls of fat can be seen in children [6]. Atherosclerotic plaques are usually located in large vessels like the aorta and medium vessels in places where they are divided into smaller branches [7]. Deposition of lipids in the vessel wall is one of the most characteristic and commonly known features of this process [5, 6]. However, the cause and factor initiating this inflammation is under investigation. Many factors are taken into account – from foetal life, maternal lipid levels during pregnancy, genetic and lifestyle factors to social status [7].

However, there have been more and more publications about contribution of microorganisms and past infections in the development of this process. It involves an immune response to inflammation as a result of bacterial or viral infection along with the acceleration of the atherosclerotic process in the vessels [5]. Therefore, this review will follow the development of the concept of atherosclerosis aetiology, focusing on the latest insights on the relationship between previous Chlamydia pneumoniae infection and the mechanism of the appearance and development of atherosclerotic changes in the arteries.

Results

Atherosclerosis etiology

Atherosclerosis is a process caused by the coexistence of many different risk factors. The most known and acknowledged ones are included in Table 1. One of the most important are genetic factors, because there is scientific evidence for heredity of predisposition to atherosclerosis, which is estimated at 40 to 60%. There are currently 60 known loci associated with atherosclerosis [8]. However, in the study of Willer et al. in which over 180,000 patients were examined, as many as 157 gene loci affecting blood lipid levels, closely related to atherosclerosis, were recognized. What's more, almost half of them have just been identified and have never been associated with lipid levels before [9]. As it turns out, regulation of HDL and LDL levels is connected with miRNA in the liver by affecting gene expression. Such a relationship was observed with miR--148a during an experiment, in which an increase in HDL and a decrease in LDL levels was visible due to a decrease in the activity of this miRNA. This probably caused an increase in the expression of the genes responsible for the coding of LDL receptor proteins. MiR-148a is not the only one miRNA that may be associated with dyslipidemia and atherosclerosis, miR-122 or miR-223 may have similar effects at various stages of lipid level regulation [10].

Another risk factor for atherosclerosis is diet and its effect on blood lipid levels. As Kuchta et al. showed after examining 42 people, whether people eat only plants or animal products significantly changes the content of individual lipid fractions in the blood serum. As a matter of fact, the people participating in the study were in the age range between 23 and 38 years old, none of them smoked or practiced sport professionally, and their BMI was within normal limits. Patients were divided into two 21-person groups. Before the study, the vegan group had to be on a diet completely devoid of animal products for a minimum of 22 months. The study lasted at least 10 months. As demonstrated, the vegan group did not differ from the second group of omnivorous patients only by the level

of HDL-C, the other results measured in serum like LDL-C and TC were significantly lower. This suggests that a plant-based diet may be an effective way to prevent atherosclerosis, while a diet containing animal-derived products may be a risk factor for atherosclerosis [11].

What is more, the effect of intestinal microflora and its composition disorders is also highlighted as a factor in atherosclerosis [12]. Emoto et al. also indicate the involvement of intestinal microflora in this process. The composition of the microflora differed between groups mainly in the amount of Lactobacillales and Bacteroidetes. Lactobacillales bacteria were at higher number in people with known atherosclerotic lesions, and there were more Bacteroidetes in healthy patients [13]. However, not only intestinal microflora may be associated with the atherosclerotic process, impaired oral microflora may also affect its course. Fåk et al. examined the composition of microflora in 92 people and found that patients without atherosclerosis vary from those with clinical signs of atherosclerosis in the amount of Anaeroglobus bacteria. A group of people with no change in their arteries had fewer of them [14].

Another interesting thing indicating bacteria's big role in atherosclerosis is that Calandrini et al., analyzing samples taken from atherosclerotic plaques in the carotid arteries, found bacterial DNA in more than 30% of them [15]. Chlamydia pneumoniae has a certain part in the etiology but still discussed.

Table 1. Atherosclerosis main risk factors [16]

Hypercholesterolemia	Hypertension
Obesity	Diabetes mellitus
Unhealthy diet	Smoking cigarettes
Endothelial inflammation	Increased procoagulant activity

The development of atherosclerotic plaque is multi-staged and does not have to be carried out in just one vessel. Various arteries may have plaques at different stages of development. The entire process begins with damage to the endothelium, i.e. the inner lamina of the artery [17, 18].

Endothelial damage promotes the adhesion of cells of the immune system, the most important of which are macrophages and lymphocytes. These cells produce pro-inflammatory cytokines, such as interferon gamma or tumor necrosis factor, and chemokines, e.g. interleukin 8. They stimulate the transmigration of leukocytes inside the vessel wall and the inflammatory process within it [8, 17, 18]. Macrophages formed from peripheral blood monocytes and other cells, e.g., myocytes and fibroblasts, use scavenger receptors to capture low-density lipoproteins. Then, LDL cholesterol undergoes chemical changes that lead to the formation of foam cells, so characteristic of atherosclerotic plaques [8, 18]. Among the substances secreted by macrophages there are also growth factors that stimulate the migration of myocytes from the middle membrane. All of these processes lead to the deposition of low-density lipoproteins, which can undergo mineralization, connective tissue formation and plaque formation [18, 19]. The atherosclerotic process is very complex and may take several or several dozen years [17].

Chlamydia pneumoniae – a significant cause of various diseases

Chlamydia pneumoniae is a common microorganism occurring widely around the globe. The presence of specific antibodies in serum of about 40–70% of people in the population overall confirms the cosmopolitan nature of this bacteria [20]. It is gram-negative and grows only in cellular lines [21]. Ch. pneumoniae is characterised by biphasic cycle because it numerously converses between extracellular EBs (infective, non-replicative elementary bodies) and intracellular RBs (replicating reticulate bodies) and replicates in inclusion vacuoles. It is very hard to eradicate the bacteria because of its intracellular cycle – most antibiotics cannot be used, though tetracyclines, macrolides, fluoroquinolones might help [22].

The infection caused by Chlamydia pneumoniae is mostly asymptomatic (60-80%). Due to its strong affinity for respiratory epithelial cells it leads to infections of upper respiratory tract: pharynx, larynx, paranasal sinuses, middle ears and lower respiratory tract: bronchi and pneumonia.

If symptoms appear they usually are mild, non-specific and chronic [21]. Many authors associate the inflammatory process with pathogenesis of coronary artery disease, atherosclerosis, vasculitis, arthritis, asthma [23].

There is evidence that Ch. pneumoniae presence has a major role in asthma, chronic bronchitis and chronic obstructive pulmonary disease (COPD) aetiology. It was found that infection of respiratory epithelial cells and macrophages cause the secretion of cytokines and activates inflammatory cells such as TNF-α, IL-1β, IL-4, IL-6, IL-8, whose role is to neutralize pathogens but can also contribute to long-term consequences [24]. Lipopolysaccharide and Heat Schock Protein 60 that Ch. pneumoniae produces can slowly change the tissue. Infectious asthma caused by it is more severe, difficult to diagnose and treat. It was revealed that Ch. pneumoniae stimulates IgE antibodies in asthmatic patients [25]. Moreover, the Nagahama study showed that seropositivity for *Chlamydia pneumoniae* along with Mycoplasma pneumoniae in Japanese population is a major risk factor for COPD [26]. There is a strong connection between chronic pulmonary diseases and cardiovascular complications that are more common in those patients and it is worth pointing out that Ch. pneumoniae often occurs in both.

Studies indicate that Ch. pneumoniae may also be a trigger in neurodegenerative diseases. Bacterial DNA was studied using PCR in post-mortem brain samples of people with dementia. Ch. pneumoniae was found near the amyloid area where cytokines were produced by glial cells and astrocytes -IL-1β and IL-1 may initialize Aβ production in Alzheimer's disease [27]. Genome analysis of Ch. pneumoniae compared strains from human with coronary heart disease and brain of person with Alzheimer's to strains available in GenBank. The goal was to study genetic differences between infection in various tissues. Some important dissimilarities were observed, especially deletions of loci probably responsible for virulence (*IncA*-like proteins, *tyrP*, *pmpG*) [28].

There is still a lot to prove in Ch. pneumoniae case. It certainly has exceptional impact on multiple human tissues and therefore whole organism. Ch. pneumoniae antibodies were found in patients' blood who

has had respiratory infection in the past [29]. Its occurrence detected in patients with so many diseases also hints that inflammation process that this bacteria evokes is indeed significant in causing slow but serious damage and dysfunction.

Chlamydia pneumoniae-induced atherosclerosis

In the early 20th century, William Osler and his associates were the first to state that the factor causing damage of the arteries is chronic inflammation process [30]. It is commonly associated with increase in blood cholesterol or an incorrect proportion of its fraction and that knowledge is widely-spread as prevention and treatment of atherosclerosis are mostly based on it. Many reports show a great part of Ch. pneumoniae's DNA and its antigen occurrence in cardiovascular diseases' etiopathogenesis, though. It gives a chance of better understanding, and so forth, starting new actions.

Chlamydia pneumoniae acts both directly and indirectly on the artery wall. It intracellulary stimulates macrophages to produce inflammatory factors, e.g. interleukins. Moreover, its antigens like Heat Shock Protein are structurally similar to human ones, what causes a cross-reaction, in which the immune system can attack both the bacteria and unfortunately its own tissue [31]. It indicates that atherosclerosis might have an autoimmune background and that Ch. pneumoniae perhaps contributes to it.

Meta-analysis including more than 10 000 patients showed that patients who were Ch. pneumoniae IgA seropositive had much higher levels of proinflammatory and prothrombotic factors such as fibrinogen, hsCRP and IL-6 than seronegative patients, both groups with atherosclerosis [32]. It gives possibility that those with Ch. pneumoniae can have a faster or greater degeneration of arteries because of presence of known initiators and promoters of the disease in a prominent amount. They can also be at better risk of severe cardiovascular consequences, what needs to be studied further.

Ch. pneumoniae's genomic DNA was detected through PCR reaction at a higher level in tissue from ascending aorta than in peripheral blood mononuclear cells. Group of patients had chronic coronary disease and were planned for CABG. Furthermore, those patients with Ch. pneumoniae in their aorta also suffered from diabetes and hypercholesterolemia [33]. Another study carried out in China found Ch. pneumoniae and Cytomegalovirus antigens at significant levels in plaque of participating patients with carotid artery stenosis, with Ch. pneumoniae antigens at 84% detection rate [34]. This proves that bacteria presence in the aorta and other arteries is not without any effect – it provokes constant changes in tissues that lead to cardiovascular diseases and can also negatively affect patients overall condition.

It is believed that not only chlamydial Heat Shock Protein 60 and interleukins but also activation of Toll-Like Receptor-4 and MAPK participates in atherosclerosis development. This is the result of Ch. pneumoniae stimulating impact on Human Vascular Smooth Muscle Cells. Furthermore, Ch. pneumoniae has a role in processes involving histones and NF-KB. Therefore, it can be seen that this bacteria affects many various reactions in human body resulting in vascular atherosclerotic degeneration [35].

Ch. pneumoniae is particularly linked to interleukin 8. IL-8 can be present in unstable plaques both with Chlamydia which can contribute to producing it in great amount [36]. Unstable plaque is very dangerous as it can tear itself away and be a cause of vascular obstruction. Heart attacks, strokes and other ischemic complications may occur. This is another trace that Ch. pneumoniae may not only contribute to atherosclerosis but also severe complications of this disease. The path showing one by one how Ch. pneumoniae infection can cause plaque formation is presented in Figure 1.

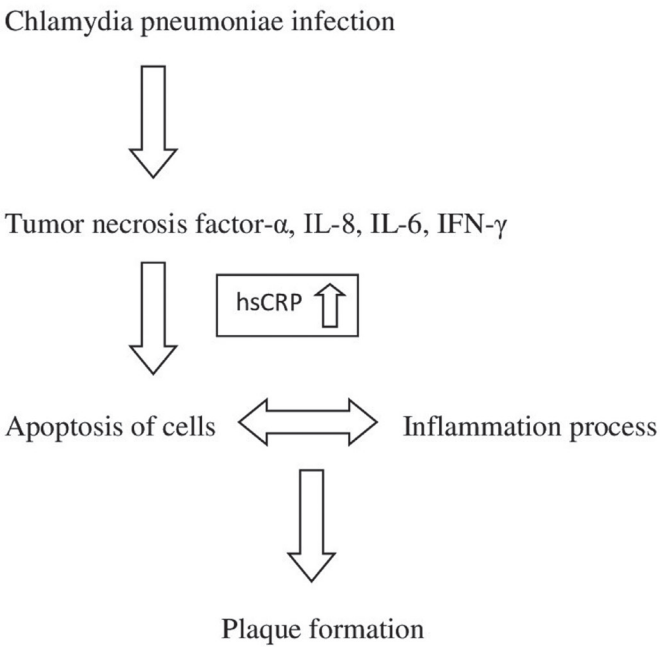

Figure 1. Scheme showing the path from Chlamydia pneumoniae infection to atherosclerosis [37]

All in all, there is no doubt that Ch. pneumoniae can have a strong, negative effect on blood vessels. It affects both structure and function of arteries mostly through chronic inflammation process and may clearly be mentioned as one of the most important among other pathogens causing atherosclerosis [38].

Discussion

Could Ch. pneumoniae alone be able to induce atherosclerosis? According to Sorrentino and Yilmaz it can in mice with ApoE deficiency. In those infected with the bacteria there was development of the conditions such like those appearing in atherosclerosis in humans as interferon γ concentration and Th1-like cells were characteristic [39].

Lantos and Endrész went one step further and used ApoB100only/LDLR−/− mice which more resemble human organisms with high cholesterol levels. They proved that Ch. pneumoniae infection aggravates atherosclerosis in the aorta compatible to the previous study [40]. Another recent study on mice that was supposed to show Murine Novovirus with Ch. pneumoniae influence on plaque formation confirmed that Ch. pneumoniae does indeed have a meaning impact as it alone enlarged the atherosclerotic obstruction in arteries by 62% in comparison with animals without infection [41].

Because of so much evidence of Ch. pneumoniae contributing to atherosclerosis it was promising that antibiotics would make a perfect testing form of treatment so thorough research was made, for example Wizard, ACES or PROVE IT-TIMI. In the WIZARD study there were almost 8000 patients after myocardial infarction included, randomly assigned to 3-month azithromycin or placebo therapy. They have been observed for a year and there was no satisfying effect on adverse clinical events such as death or recurrent heart attack due to exacerbation of coronary artery disease [42]. In ACES the time has been extended to one year of taking azithromycin and in PROVE IT-TIMI to two years with the antibiotic changed to gatifloxacin, though. Unfortunately, it did not meet scientists expectations because of the lack of effectiveness [43].

If antibiotics capable of Ch. pneumoniae eradication did not cause the clinical improvement in atherosclerosis treatment then Ch. pneumoniae as important etiologic factor loses its meaning. Suggestions escalated that the role of Ch. pneumoniae in this civilisation disease is in fact small as it mostly depends on other confirmed risk factors e. g. lipids. As a consequence the number of studies on this subject has decreased. On the other hand, different point of view has appeared. In those studies antibiotics were given to people with already developed atherosclerosis and often after myocardial infarction. There is a strong possibility that antibiotics could have worked in a group of children, as Ch. pneumoniae infection firstly appears in the young age, in order to prevent atherosclerotic acceleration in time [44].

So if antibiotics did not work then should studies concerning fight against Ch. pneumoniae to treat atherosclerosis end? Innovative thinking paths are necessary regarding to treatment, so it was revealed that vaccines may be a real breakthrough. Immunization with recombinant chlamydial protease-like activity factor (rCPAF), in particular with Il-12, reduces atherosclerosis development in mice infected by Ch. pneumoniae and on high fat diet through inducing specific antigens production [45].

Even though some big studies using antibiotics failed to prove atherosclerosis attenuation, there is still a great chance of them being useful in prevention of this disease. Furthermore, treatment based on Ch. pneumoniae role in atherosclerosis is still possible thanks to immunization and there is definitely a lot to investigate. It proves that further trials are needed regarding Ch. pneumoniae importance in initiation and progression of inflammation process of the arteries and atherosclerosis associated with it.

Conclusions

Atherosclerosis is a multifactorial process – many risk factors are already known but its cause cannot be clearly determined. The impact of some dangers leading to it can be reduced or completely eliminated. Knowing that there is a relationship between the development of the atherosclerotic process and the presence of Chlamydia pneumoniae will allow medics to better monitor the patient and implement earlier and more effective treatment.

Because of the universal prevalence of Chlamydia pneumoniae, infections caused by it are quite common, but in most cases without clinical symptoms. However, by stimulating the production of inflammatory factors they have a significant impact on the functioning of many tissues. A correlation has been demonstrated between the past infection and the risk of occurrence and severity of chronic respiratory diseases, which may be associated with an increased likelihood of cardiovascular complications. In addition, due to the long-term asymptomatic inflammatory

process, it can happen not only in the respiratory tract, but also in nerve tissue or vascular wall. Ch. pneumoniae induces similar immunological reactions that are observed in atherosclerosis, and also worsens the course of an ongoing process.

Determining the levels of inflammatory cytokines, especially Il-8 or TNF-α so strongly associated with both Chlamydia pneumoniae infection and atherosclerosis can be useful in assessing cardiovascular risk and preventing myocardial infarction and other atherosclerotic diseases. However, antibiotic therapy of existing lesions in patients with Ch. pneumoniae did not give satisfactory results, but perhaps it would be effective as a prophylaxis for infections with this pathogen in children. Therefore, research is being conducted into the possible use of vaccinations and their effectiveness in the prevention of atherosclerosis. To sum up, many processes determining atherosclerotic damage are not fully known yet, so staying open to new research all the time is a forward-looking approach.

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