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Pathogenesis of *Chlamydia pneumonia* Persistent Illnesses in Autoimmune Diseases

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1. Introduction

Infectious agents have been implicated in the pathogenesis of many autoimmune diseases. In most of these diseases, including those in which specific organisms are known to play a role, the details of pathogenesis remain incompletely defined. Recent studies have aimed to isolate bacterial and viral pathogens from patients with autoimmune diseases, efforts have been made to further define the host immune response to infection, and there have been attempts to develop improved methods of diagnosis and treatment of infectious diseases affecting the Immune system. More recently, *C.pneumonia* has been linked to many autoimmune diseases [20].

Chlamydia pneumoniae is an important respiratory pathogen associated with 5% to 10% of community-acquired cases of pneumonia, pharyngitis, bronchitis, and sinusitis. Infection is most common among children 5 to 14 years of age, and the majority of adults have serologic evidence of past infection. Antibodies have also been found frequently in people in many countries worldwide. The bacterium is an obligatory intracellular pathogen that has the tendency to cause persistent infection, and may drive a chronic inflammatory reaction in coronary vasculature or other tissues. The characteristic feature of all chlamydial species is their tendency to establish a long-lasting parasitic relationship with the host and chronicity is a hallmark of *Chlamydia* infection. Adults are particularly prone to have prolonged illness, with relapses and secondary infections. *Chlamydiae* are known to infect macrophages and monocytes as well as epithelial cells. *C. pneumoniae* also infects endothelial and smooth muscle cells of blood vessels. Tissue injury in all chlamydial diseases appears to be immune mediated [27].

Only one serovar or immunotype has been found, Molecular studies have found only small and probably inconsequential differences among isolates. Despite its recent isolation, it should be said that *C. pneumoniae* is not a new organism. It was not found earlier because it is difficult to isolate and to keep in continuous culture. Retrospective serological studies provides evidence that *C. pneumoniae* was active for years before its isolation. Much of the knowledge of the epidemiology of *C. pneumoniae* infection has been derived from serologic studies utilizing the *C. pneumoniae*-specific microimmunofluorescence (MIF) test. More recent improvements in isolation techniques and the application of the PCR have also

greatly improved the capability to detect the organism in clinical specimens and facilitated more detailed microbiologic studies [40].

This review is a brief discussion on recent studies about the association of *C. pneumoniae* infection with illnesses affecting the immune system, with an emphasis on the autoimmune diseases.

2. Autoimmune disorders and infection

2.1 Autoimmune diseases

An autoimmune disorder is a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue. The immune system is an amazing collection of biological processes designed to defend the body against invasion by infectious pathogens and tumor cells. This system includes innate, adaptive and memory responses that are constantly activated, adapted and improved to meet the challenge of evading pathogens more efficiently. Normally the immune system's army of white blood cells helps protect the body from harmful substances, called antigens. Examples of antigens include bacteria, viruses, toxins, cancer cells, and blood or tissues from another person or species. In addition, the immune system must be tolerant and distinguish between self and nonself, so that substances that are identified as nonself stimulate an immune response, while no harm is inflicted upon self. However, as in any complex system, malfunctions occur, leading to diseases of immune dysregulation. In patients with an autoimmune disorder, the immune system can't tell the difference between healthy body tissue and antigens. The result is an immune response that destroys normal body tissues. This response is a hypersensitivity reaction similar to the response in allergies. In allergies, the immune system reacts to an external substance that it normally would ignore. With autoimmune disorders, the immune system reacts to normal body tissues. Furthermore autoimmunity is a consequence of the breakdown of self-tolerance; the result is an attack of the immune system on various organs and tissues as if they were foreign invaders [61].

There are more than 80 different types of autoimmune disorders. Autoimmune diseases have many causes. Genes, notably genes encoding cell-surface proteins that display peptides for immune recognition, the major histocompatibility complex (MHC), the environment, and the microbial diversity within the human body determine the susceptibility to autoimmune diseases. One mechanism by which infection is linked to the initiation of autoimmunity is termed molecular mimicry. Molecular mimicry describes the phenomenon of protein products from dissimilar genes sharing similar structures that elicit an immune response to both self and microbial proteins. Auto immune diseases (ADs) are the third leading cause of morbidity and mortality, after heart disease and cancer, in the industrialized world. What causes the immune system to no longer tell the difference between healthy body tissues and antigens is not clearly known. Researchers are looking into the role of different factors in the development of autoimmune disorders. It seems that some microorganisms and drugs may trigger some of the changes, especially in people who have genes that make them more likely to get autoimmune disorders. One theory is that, a combination of genetic, immunologic, hormonal and environmental factors, comprising what is known as 'the mosaic of autoimmunity', is required for autoimmune disorders to develop [59]. Among these key elements, the impact of infections on the development of

autoimmunity is substantial, and various mechanisms have been suggested to explain this relationship. In recent years, the compound interplay between infections and autoimmunity has been studied extensively [58, 59].

An autoimmune disorder may result in destruction of one or more types of body tissue, abnormal growth of an organ, or changes in organ function. Organs and tissues commonly affected by autoimmune disorders include red blood cells, blood vessels, connective tissues, endocrine glands such as the thyroid or pancreas, muscles, joints, and skin.

Main human autoimmune disorders are Multiple sclerosis, Rheumatoid Arthritis, Scleroderma, and Neurologic autoimmune diseases. With the exception of multiple sclerosis, these diseases are rare. Autoimmune disorders affect people of all genders, races, and ages, but certain people have an increase risk of developing autoimmune disorders. Main risk factors for autoimmune disorders are Gender, Age, Ethnicity, Family history of autoimmune disorders, Exposure to environmental agents and previous infection.

2.2 Autoimmune disorders induced by infection

The high percentage of disease-discordant pairs of monozygotic twins demonstrates the central role of environmental factors in the etiology of autoimmune diseases. Efforts were first focused on the search for triggering factors. The study of animal models has clearly shown that infections may trigger autoimmune diseases, which can also determine its clinical manifestations. Most infectious agents, such as viruses, bacteria and parasites, can induce autoimmunity via different mechanisms. In many cases, it is not a single infection but rather the 'burden of infections' from childhood that is responsible for the induction of autoimmunity. The development of an autoimmune disease after infection tends to occur in genetically susceptible individuals. By contrast, some infections can protect individuals from specific autoimmune diseases [50].

The observation that infection can precipitate an autoimmune disease dates back more than a century. The first human autoimmune disease described, paroxysmal cold hemoglobinuria, was thought of as a late consequence of syphilis, and rheumatic fever is still associated with preceding streptococcal infection.

Bacterial and viral infections are commonplace in a variety of autoimmune and chronic illnesses such as the chronic fatigue syndrome; fibromyalgia syndrome, Gulf war illnesses and rheumatoid conditions. Much attention is focused at present on the role of bacteria and the possible mechanisms of their involvement in the pathogenesis of several diseases. The route of infection and penetration, and the immune responses of the host can not only make any bacterial infection pathogenic but probably can also determine the aggressiveness of the disease and the chance for full recovery [21].

A wide variety of bacterial infections have been associated with autoimmune disorders. For example *M.pneumonia, M.salivarium, and M.fermentas*, has been strongly associated with rheumatoid arthritis. *Proteus mirabilis* has been implicated in the pathogenesis of rheumatoid arthritis and osteoarthritis. Enterobacteriaceae family is associated with some autoimmune conditions such as Kawasaki syndrome and Graves disease. Genitourinary *mycoplasma* infection has been associated with systemic lupus erythematosus. *Campylobacter jejuni, Haemophilus influenza and M. pneumoniae* have been implicated as possible causative of

Guillain-Barre syndrome .Recently it has drawn attention to the putative link of bacterial nasopharyngeal infections with optic neuritis, optochiasmatic arachnoiditis and Multiple Sclerosis. More recently serology and PCR(polymerase chain reaction) have provided ample evidence of *Chlamydia pneumonia* ,*Borrelia burgdoferi*, *Mycoplasma* species, human herpesvirus-1 and -6 among others in MS, Amyoyrophic Lateral Sclerosis, Alzheimer's and Parkinson's diseases. A tentative relationship between MS and streptococcal infection has been suggested. And finally acute rheumatic fever, which presents several weeks after infection with *Streptococcus pyogenes* in which, the Molecular resemblance between the bacterial M-protein and human glycoproteins results in a breakdown of self-tolerance in genetically susceptible individuals [24, 58].

Post-infection autoimmunity can be induced by multiple mechanisms, such as molecular mimicry, epitope spreading, bystander activation, viral persistence and polyclonal activation. The induction of a Guillain-Barré syndrome in rabbits after immunization with a peptide derived from *Campylobacter jejuni* is explained by mimicry between *C. jejuni* antigens and peripheral nerve axonal antigens. Triggering of autoimmunity is not always a hit and run event, but rather a cumulative process. The immune system is affected by repeated infections from childhood, and in immune-sensitive individuals, a breakthrough point might occur when the infection burden crosses a crucial level. This breakthrough point might be reached when a specific pathogen load, immune load (i.e. antibody titer) or a unique combination of pathogens is established [23].

Even though there are many tests available, the MIF test is the only currently acceptable serologic test for detection of *C. pneumoniae* antibodies and is widely accepted as the "gold standard" in *C. pneumoniae* Serodiagnonosis [18]. Serologic tests detect antibodies to a specific micro-organism, which indicates that infection with the micro-organism, took place at some point in time. However, absolute proof of the micro-organisms actual involvement in the process atherosclerosis could only come from demonstrating its presence in the vascular wall.

3. *Chlamydia pneumoniae* and autoimmune diseases

3.1 Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory disease leading to disseminated lesions of the central nervous system resulting in both somatomotor and autonomic disturbances. Somatomotor and autonomic disturbances occur with similar frequency. Multiple sclerosis is the most common demyelinating disease of the human central nervous system (CNS), principally affects adults aged 18–50 years. Women are generally affected earlier and more frequently than men. Most patients present with a relapsing disease, progressing over 10– 15 years to a chronic phase with increasing difficulty in movement and co-ordination.

The pathological hallmark of MS is the demyelinating plaque that represents an area of demyelination and gliosis around blood vessels. Acute lesions show perivascular lymphocytic infiltration with infiltration of macrophages and phagocytosis of myelin membranes. Underlying axons are relatively spared, but are nonetheless affected by the inflammatory process; leading to irreversible damage. Current opinion favors the notion that MS is an autoimmune disease directed against self-neural antigens [57].

The disorder is most commonly diagnosed between ages 20 and 40, but can be seen at any age. It is caused by damage to the myelin sheath, the protective covering that surrounds nerve cells. When this nerve covering is damaged, nerve impulses are slowed down or stopped. The nerve damage is caused by inflammation. Inflammation occurs when the body's own immune cells attack the nervous system. Repeated episodes of inflammation can occur along any area of the brain, optic nerve, and spinal cord. People with a family history of MS and those who live in a geographical area where MS is more common have a slightly higher risk of the disease. The disease usually occurs sporadically and studies of identical twins in which one has MS have demonstrated that it occurs in only 30% of second twins [57].

Additional evidence for the role of infection in MS is provided by the presence of increased levels of IgG and the presence of oligoclonal bands with alkaline isoelectric points on electrophoresis gels. Oligoclonal bands occur in. 95% of MS patients, but are also seen in 10% of patients with other infectious diseases of the CNS. This pattern of increased IgG and oligoclonal bands is found almost exclusively in CNS disorders of infectious origin and is thought to represent an intrathecal immune response to an infectious agent with the oligoclonal bands representing antibodies synthesized within the CNS [57]. The bacterium may act to trigger the autoimmune process because antigenic mimicry or from an expansion of self auto reactive T cell clones in response to bacterial or viral superantigens [58].

Chlamydia pneumoniae is the latest pathogen to be associated with MS. A case of CNS infection with *C. pneumoniae* in a patient with rapidly progressive MS has been reported. Antimicrobial therapy directed against this pathogen was accompanied by marked neurological improvement [60]. Subsequent studies found that *C. pneumoniae* is present in the CSF of patients with newly diagnosed relapsing, remitting MS and in patients with progressive MS, but not in other neurological disease controls [61].

Although there is a strong association between *C. pneumoniae* and MS, its role remains unproven. Before a causal relationship with the development or progression of MS can be claimed, the relapsing remitting nature of the disease that later develops into a chronic progressive phase must be explained satisfactorily. Moreover, the immune abnormalities in CSF (increased immunoglobulin synthesis and oligoclonal bands), the sex bias and the geographical distribution of the disease must all be addressed. One of the hallmarks of chlamydial infection is its tissue persistence and the development of chronic infection. *Chlamydiae* are known to infect macrophages and monocytes as well as epithelial cells. *C. pneumoniae* also infects endothelial and smooth muscle cells of blood vessels. Tissue injury in all chlamydial diseases appears to be immune mediated [66].

Recently, it has showed the specificity of intrathecal antibody response to *C. pneumoniae* antigens in relapsing remitting and progressive MS patients [74]. In most of MS patients studied, an elevated antibody titre to *C. pneumoniae* EB antigens was seen and was present in the CSF of them [74]. Increased antibody titres to *C. pneumoniae* were seen in about 20% of other neurological disease controls [24, 38].

Studies carried out by many researchers support a role for *C. pneumoniae* infection of the CNS in the pathogenesis of MS. However, the similarities in clinical disease pattern between known chlamydial diseases and MS do not conclusively establish a causal relationship between *C. pneumoniae* infection of the CNS and the development or progression of MS.

Further evidence to confirm or repudiate the presence of *C. pneumoniae* infection of the CNS in MS patients is needed. Evaluation of brain tissue from MS patients by immunochemical and in-situ PCR staining for *C. pneumoniae* is also necessary. If such studies show *C. pneumoniae* infection of microglial cells or oligodendrocytes in MS plaque or tissues adjacent to plaques, clinical neurologists can then consider treating MS patients with long term antimicrobial agents. The design of an appropriate therapeutic trial may be difficult because of the current absence of experimental animal models for either MS or for *C. pneumoniae* induced inflammation and demyelination of the CNS. Only a well designed therapeutic trial with sufficient statistical power is likely to provide additional answers concerning the relationship between *C. pneumoniae* infection of the CNS and the development or progression of MS [38].

As a large number of individuals are infected with the organism, it is possible that *C. pneumoniae* is the inciting agent of MS in genetically susceptible individuals. Activation of perivascular and parenchymal microglial cells along with the attendant biochemical mediators would lead to destruction of the surrounding myelin. An infectious agent that targeted microglial cells and endothelial cells would be a likely candidate in MS [49].

C. pneumoniae IgM positive cases were more frequent among the patients with rheumatoid arthritis , systemic lupus erythematosus, dermatomyositis/polymyositis , myeloperoxidase-antineutrophil cytoplasmic autoantibody -associated vasculitis , adult onset of Still's disease and giant cell arteritis/Takayasu arteritis than among the controls [24].

3.2 Stroke, an immunopathogenic complication of persistent *C. pneumonia* illness

Etiology of ischemic stroke is multi factorial and infections have emerged as one among them. In the last decade, several reports have shown the association of chronic *C. pneumoniae* infection with atherosclerosis and thrombosis and many studies have incriminated *C. pneumoniae* in the causation of coronary heart disease, stroke and asymptomatic carotid atherosclerosis.

In fact, patients having an infection within a week before the onset of stroke might develop cortical middle cerebral artery infarcts, cardioembolic infarcts and arterial dissections suggesting a differential effect of infection. In older patients, various conventional risk factors (diabetes, hypertension, hypercholesterolemia, etc) play an important role in stroke etiopathogenesis. However, younger patients (aged <45years) usually lack these risk factors, and infections, especially in developing countries, may assume significance [8, 9]. It is therefore relevant to look for the role of infection in contributing to various subgroups of ischemic stroke in young patients [8].

Bandaru *et al* found an association between the presence of *C. pneumoniae* antibodies and ischemic stroke among young Indian patients. They found that positive serum IgG and IgA antibody titer by microimmunofluorescence (MIF) test, against *C. pneumoniae* was significantly more in ischemic stroke patients compared to age and sex matched control subjects [8,9]. This is in agreement with previous studies where *C. pneumoniae* antibody positivity has been noted in young stroke patients [3, 47].

In Cameroon, Njamnshi AK *et al* demonstrated that *C. pneumoniae* infection is significantly associated with ischemic stroke in patients in the < 50 years age group compared to matched

controls [47]. Another study also demonstrated that *C. pneumoniae* seropositivity can increase the risk of stroke in young patients aged below 55 years in which, *C. pneumoniae* seropositivity in all ischemic stroke subgroups except stroke of indeterminate etiology is found [8].

C. pneumoniae infection causes atherosclerosis of large arteries by infecting the vascular endothelial cells, activation of the NF-κβ, up regulation of procoagulant activity (tissue factor, plasminogen activator inhibitor), increased platelet count, adhesion molecules and finally thrombosis formation. The positivity of *C. pneumoniae* antibodies in nonatherosclerotic strokes like small artery disease and stroke of other determined etiology caused by pathophylogical changes due to lipohyalinosis or hypercoagulability may be an epiphenomenon.

CRP is a marker of inflammation. Several studies have found that *C. pneumoniae* infection could contribute to elevation of CRP levels and to the instability or progression of atherosclerotic plaques. In the study of Bandaru et al, both *C. pneumoniae* and CRP positivity was found in 29% of patients and it was significantly associated with stroke compared to controls subjects [8]. Hasan found that Chronic *C. pneumoniae* infection demonstrated by positive IgA-type antibody can be considered a significant risk for ischemic stroke [31].

If persistent *C. pneumoniae* infection contributes to vascular events such as stroke, it is interesting from a therapeutic perspective. Although *C .pneumoniae* may contribute to the risk of stroke directly, in most cases, it acts in concordance with the conventional risk factors. In younger individuals with ischemic stroke in whom *C. pneumoniae* found to be a risk factor, eradication of infection by antibiotic treatment may decrease the risk of stroke [3,8,9, 47].

3.3 Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Symptoms include progressive memory loss, decreased cognition, problems with spacial and perceptual recognition, and impairment of daily living. The hallmark of Alzheimer's disease is the extracellular accumulation and deposition of insoluble amyloid, to be found in the parenchyma in the form of amyloid plaques and in meningeal and cerebral vessels as a congophile angiopathy. Amyloid plaques and neurofibrillary tangles are characteristic, but not specific to Alzheimer's disease. Similar changes can be found in healthy ageing processes and in various other neurodegenerative diseases. It is common to differentiate between an early-onset, familial Alzheimer's disease(FAD) with an established genetic etiology, representing only about 5% of all cases, and the more typical late-onset, sporadic Alzheimer's disease (LOAD)with an age of onset above 65 years and no clear pattern of inheritance [39]. The development of LOAD, the most prevalent form of AD, is believed to be a multifactorial process that may also involve infections with bacterial or viral pathogens. After the first report on the presence of *C. pneumoniae* in brains of patients with AD appeared in 1998, this bacterium has most often been implicated in AD pathogenesis. However, while some studies demonstrate a clear association between *C. pneumoniae* infection and AD, others have failed to confirm these findings [38].

Sporadic, late-onset Alzheimer's disease (LOAD) is actually a non-familial, progressive neurodegenerative disease that is now the most common and severe form of dementia in the

elderly. That dementia is a direct result of neuronal damage and loss associated with accumulations of abnormal protein deposits in the brain. Great strides have been made in the past 20 years with regard to understanding the pathological entities that arise in the AD brain, both for familial AD (approximately 5% of all cases) and LOAD (approximately 95% of all cases [39].

Some indirect evidence seems to suggest that infection with *C. pneumoniae* might be associated with the disease. Nucleic acids prepared from those samples were screened by polymerase chain reaction (PCR) assay for DNA sequences from the bacterium and showed that brain areas with typical AD-related neuropathology were positive for the organism in 17/19 AD patients [7, 26, 39]. Electron- and immunoelectron-microscopic studies of tissues from affected AD brain regions identified chlamydial elementary and reticulate bodies, but similar examinations of non-AD brains were negative for the bacterium. Culture studies of a subset of affected AD brain tissues for *C. pneumoniae* were strongly positive, while identically performed analyses of non-AD brain tissues were negative [39]. Reverse transcription (RT)-PCR assays using RNA from affected areas of AD brains confirmed that transcripts from two important *C. pneumoniae* genes were present in those samples but not in controls. Immunohistochemical examination of AD brains, but not those of controls, identified *C. pneumoniae* within pericytes, microglia, and astroglia [7, 26]. Further immunolabelling studies confirmed the organisms' intracellular presence primarily in areas of neuropathology in the AD brain. Thus, *C. pneumoniae* is present, viable, and transcriptionally active in areas of neuropathology in the AD brain, possibly suggesting that infection with the organism is a risk factor for late-onset AD [41]. In other study, Immunohistochemical analyses showed that astrocytes, microglia, and neurons all served as host cells for *C. pneumoniae* in the AD brain, and that infected cells were found in close proximity to both neuritic senile plaques and neurofibrillary tangles in the AD brain [26, 41].

The importance of inflammation in the pathogenesis of neurodegenerative disorders, such as Alzheimer's disease, is increasingly being recognized. Although amyloid-beta is considered to be one of the main initiators of these inflammatory processes, some reports suggest that brain infections may also contribute or even initiate the neuroinflammation [39]. Recent data showed the role of *C. pneumoniae* infection in neuroinflammation and its potential contribution to the pathogenesis of Alzheimer's disease [7].

In an experimental trend, amyloid deposits resembling plaques found in Alzheimer's disease (AD) brains were formed in the brains of non-transgenic BALB/c mice following intranasal infection with *C. pneumoniae*. The mice were infected at 3 months of age with *C. pneumoniae* isolated from an AD brain. Infection was confirmed by light and electron microscopy in olfactory tissues of the mice. *C. pneumoniae* was still evident in these tissues 3 months after the initial infection indicating that a persistent infection had been established [41].

Medications (for example, antibiotics and anti-inflammatory drugs) prescribed to older individuals could affect the phenotypic and persistent nature of the organism, especially in the brains of patients with AD [11]. The proinflammatory response following infection may result in damage to *C. pneumoniae* as a result of evoked bacteriostatic events such as free radical damage in the tissues and/or nutrient starvation of the organisms [39]. In this regard, typical and atypical forms of *C. pneumoniae* were observed in the AD-affected brain. The main phenotypical differences were exhibited in the overall shape and size of the

organisms, but immunoreactivity to the organism in the brain was similar to that of *C. pneumoniae* laboratory strains [4].

Inflammation is common in the AD brain in areas of neuropathology. This inflammation has been advanced as a pathogenic mechanism in the disease. Indeed, inflammation has been implicated as an important factor in a number of diseases, and one study indicated that administration of nonsteroidal antiinflammatory drugs could be beneficial in treating AD [11]. Because chlamydial infection engenders a strong inflammatory response, infection by *C. pneumoniae*, in part, may be responsible for the inflammation observed in the AD affected brain [39]. The results of Balin study demonstrated the frequent infection of microglia and astroglia with *C. pneumoniae* in the AD-affected brain [7]. Intriguingly, an animal model, in which low-dose infusion of LPS has been used, revealed remarkable parallels with AD inflammation including APP induction, increased cytokine production with microglial reactivity, and temporal lobe pathology [41].

Microglia are the resident tissue macrophages of the brain, and once activated they, like astroglia, are a source of inflammatory cytokines, including IL-1, TNF, and IL-6. Another study also showed that the infected cells in the AD-affected brains were microglia, astroglia, perivascular pericytes, and macrophages. These findings and an in vitro studies suggest that the glial cells and blood monocytes that traffic into the brain are primarily infected with *C pneumoniae* [39].

The fundamental question that must be answered is whether this organism could be a causative agent or an opportunist that finds its way into damaged tissues. In either case, the organism's presence in AD can affect aspects of symptomatology and progession that have their roots in the inflammation and blood vessel damage currently thought to play significant roles in this disease.

3.4 Vasculitis induced by *Chlamydia pneumoniae*

3.4.1 Giant cell arteritis, polymyalgia rheumatica, temporal arteritis

The possibility of infectious triggers stimulating the development of inflammatory vascular diseases has generated much recent interest. Giant cell arteritis (GCA) is a vasculitis disease affecting medium- to large-sized arteries. The disease is an inflammation of these arteries, mainly of the outermost of their three layers. It is known to be associated with previous upper respiratory tract symptoms. The occurrence of cases is often clustered in certain time periods and geographic locations. It is primarily a disease of the elderly, and is more common in women than in men. Fever of unknown origin is one of the symptoms along with polymyalgia rheumatica (PMR), a related clinical syndrome, that is strongly associated with DR4 positivity [43, 44].

Several recent studies in which activated CD41 T cells were identified in arteries of patients with GCA have strongly suggested that this disease might be antigen driven although the relevant antigens have not been identified as yet. In the search for the disease-inducing antigens in GCA, a number of different parameters have been suggested to be important. For example, the clustering of cases in specific time periods and in particular geographic locations indicates that in addition to genetic predispositions for the disease, environmental or seasonal factors may be significant. Moreover, GCA and polymyalgia rheumatica (PMR)

are related clinical syndromes that affect the elderly. This association is supported by the close similarity in the clinical patterns of both, and the striking association of both with DR4 positivity [43, 44, 45].

Importantly, upper respiratory tract symptoms are often recognized as part of the syndrome in both GCA and PMR. In this respect, some reports have suggested that *Chlamydia pneumoniae* might be involved in the pathogenesis of vasculitis. In clinical practice, it is a common observation that the onset of so-called noninfectious vasculitis is often preceded by symptoms of upper respiratory tract infection, although a specific infecting agent is only occasionally recovered in laboratory analysis of such patients. In addition, a number of recent studies have indicated renewed interest in assessing the association between atherosclerosis and vasculitis [44, 45].

Several publications have addressed the interaction among infection, inflammation, and traditional risk factors in atherosclerosis and coronary artery disease [43]. Some clinical and laboratory studies have demonstrated the presence of *C. pneumoniae* in atherosclerotic tissues from diverse anatomic locations, suggesting that this bacterium may be involved in the pathogenesis of that disease [10, 58].

Two studies have presented evidence of a coincidence of cyclic fluctuations of Chlamydia pneumoniae epidemics and cases of GCA [52, 53]. Really conflicting data exist regarding the role of C. pneumoniae in the pathogenesis of GCA. Some authors found a strong correlation between GCA and detection of C. pneumoniae [51]. In another study, 8 of 9 GCA patients were PCR-positive for *C. pneumoniae*, while the only one of nine controls who was positive for *C.pneumonia* had respiratory symptoms [51]. In some of the tissue specimens, *C. pneumoniae* was found outside of cells, "possibly suggesting that the organism was viable and undergoing active vegetative growth in temporal artery tissues in GCA patients" [52, 53].

Positive correlation between the presence of *Chlamydia pneumoniae* in temporal artery biopsy specimens and the diagnosis of temporal arteritis (TA) is found in the study of Regan *et al* using sensitive and specific PCR. Analyses showed that all 90 patients were confirmed to have met the American College of Rheumatology classification criteria for TA [51]. The results of this study and study of Cooper et al [15] do not support a role for *C. pneumoniae* in the pathogenesis of TA.

Kaperonis *et al* investigated the association of inflammation and *Chlamydia pneumoniae* infection with the presence and severity of peripheral arterial disease. This study supports the hypothesis that inflammation (CRP) and chronic *C. pneumoniae* infection (IgA seropositivity), have an important role in lower limb atherosclerosis and correlate with the severity of the disease [37].

3.4.2 Vascular dementia

Vascular dementia is characterized by a loss of cognitive function and social adaptive functions in individuals with cerebrovascular disease. Vascular dementia is the second most common cause of dementia (second only to Alzheimer's disease) and accounts for 10% to 15% of all cases. The clinical presentation of this illness is variable, depending on the site and extent of the lesion or infarct. The pathogenesis of vascular dementia has not been well defined. Chronic inflammation and cytokine dysregulation may play a role similar to that seen in Alzheimer's disease.

Recent data from serological and PCR studies support an association between C. pneumoniae and some cerebrovascular disease. *C.pneumonia* has been associated with stroke, transient cerebral ischemia, and atherosclerosis in the middle cerebral artery in both prospective and case-control studies [13, 64]. Since stroke is an important precursor to vascular dementia, these data raise the possibility that *C.pneumonia* infection may also be a risk factor for vascular dementia.

C.pneumonia serology is an imperfect test of C. pneumoniae exposure and chronic infection. First, the high prevalence of *C.pneumonia* exposure makes it difficult to detect true serological differences between cases and controls. Second, it is unclear what the appropriate serological cut-offs should be for identifying exposure versus chronic infection or recent infections [18]. As a result, different groups have used different criteria making comparisons across studies more difficult. However, the importance of this inconsistency is unclear.

There is an extensive literature supporting an association between *C.pneumonia* and atherosclerosis. Although the majority of these studies initially focused on coronary heart disease [10, 15, 16]. More recent evidence also supports an association with stroke [14]. However, the clinical importance of this association is uncertain. Carusone *et al*, found no significant association between elevated or high C. pneumoniae specific IgG or IgA antibodies and vascular dementia [13]. In this study, the odds ratio estimate for IgA titres was slightly higher than IgG titres, but not statistically different. The meaning of this difference is uncertain. Danesh *et al* suggest that these differences are likely due to chance, selection biases, or selective emphasis on particular reports [16]. The odds ratio estimate for IgA titres is also slightly higher than IgG titres, but not statistically different. Carusone *et al* suggest that the odds ratio estimates for elevated IgA and IgG antibodies do not definitively rule out an association between antibodies and vascular dementia because the relatively small sample[13]. Other studies have suggested that IgA titres are more strongly associated with disease outcomes because they are a better indicator of chronic *C.pneumonia* infection [14].

It is now widely believed that vascular risk factors are also associated with Alzheimer's disease and Alzheimer's and vascular dementia may share many common clinical and pathological characteristics [39]. A number of studies have examined the association between Alzheimer's disease and *C.pneumonia* infection. Balin *et al* found an extremely high association between the presence of *C.pneumonia* in post-mortem brain samples and late-onset Alzheimer's disease [7]. However, more recent studies have not repeated these findings one study has looked for *C.pneumonia* in brain samples of vascular dementia patients. This study, like the later AD studies, did not identify *C.pneumonia* in any of the brain samples [72]. These results suggest that the presence of *C.pneumonia* in the brains is not strongly associated with late-onset Alzheimer's disease or vascular dementia.

Inflammatory responses are also known to be associated with cardiovascular disease and have recently been implicated in dementia. Elevated levels of serum C-reactive protein (CRP), a non-specific marker of inflammation, predict cardiovascular disease and dementia, and have been associated with stroke patients [73]. Although CRP was originally thought to be produced almost exclusively by hepatocytes, CRP is now known to be synthesized in brain cells and upregulated in Alzheimer tissue [73].

3.5 Atherosclerosis and coronary artery disease

An association between coronary artery disease and other Atherosclerotic syndromes and *C. pneumoniae* infection has been suggested by both seroepidemiologic studies and the demonstration of the presence of the organism in athromatous plaque. The initial study indicating a possible association between *C. pneumoniae* and coronary artery disease was performed in Finland and showed that patients with coronary artery disease were significantly more likely to have serologic evidence of past infection with TWAR than were controls [55].

Morphologic and microbiologic evidence of the presence of *C. pneumoniae* in athermanous plaques has been obtained by electron microscopic studies of coronary atheroma, immunocytochemical staining and PCR testing of coronary, carotid, and aortic atheroma [60]. The organism has also been demonstrated in atheromatous tissue removed from patients by directional coronary atherectomy and was found more commonly in restenotic lesions than in primary lesions [12, 68]. Autopsy specimens from young persons (15 to 35 years of age) has offered the opportunity to study coronary arteries from persons without atherosclerosis, an opportunity for control material not available in older adults [12, 68]. The organism was not detected by PCR or immunocytochemical staining in 31 coronary artery specimens that showed no atheroma but was demonstrated in 2 of 11 specimens showing probable early lesions (intimal thickening) and in 6 of 7 specimens with developed atherosclerotic plaques [33]. More recently, *C. pneumonia* seropositivity was associated with enhanced intima-media thickness of arteries. While these studies clearly associate TWAR organisms with atheromatous plaques, the role of TWAR infection in the pathogenesis of atherosclerosis is unknown [10, 36].

Three types of evidence support the association of *C. pneumoniae* with atherosclerosis including seroepidemiological studies, direct detection of bacterial DNA or antigen, or both, in atherosclerotic lesions and isolation of the organism from athermanous tissue. Following the initial report of Saikku *et al* demonstrating an association of *C. pneumoniae* antibody with myocardial infarction and coronary heart disease [55], there have been more than 50 studies demonstrating a sero-epidemiological association between *C. pneumoniae* and cardiovascular disease. The strongest evidence for an association of *C. pneumoniae* with atherosclerosis has been the demonstration of *C. pneumoniae* by PCR, immunocytochemical staining and electron microscopy in atherosclerotic lesions and culture of the organism from atheromata [40, 70]. Within the atherosclerotic lesion, the organism has been detected in foam cells derived from macrophages and smooth muscle cells, a hallmark of early lesion formation, and also in endothelial cells. Although the percentage of atherosclerotic lesions in which the organism has been found covers a wide range and correlation between different detection methods has not been good, more than 45 peer-reviewed publications have confirmed the initial report of Shor *et al* demonstrating the organism in human of 272 atherosclerotic tissues tested and was not found in any of the 52 normal arteries tested [60]. Moreover, *C. pneumoniae* has not been detected in other granulomas, with the exception of sarcoid tissue, and has been found more frequently in atherosclerotic lesions than in other tissues from the same person, suggesting that the organism has a tropism for atheromas. These cumulative observational studies leave no question that *C. pneumoniae* is present in atherosclerotic lesions. Defining the pathogenic mechanisms by which *C. pneumoniae* infection could contribute to atherogenesis must be more investigated.

C. pneumoniae may infect circulatory components, which may attach to the endothelium and smooth muscle cells and kill them by apoptosis. The probable molecular mechanism of atherosclerosis pathogenesis can be explained by up-regulation of expression of heat shock protein 60 (HSP-60) by C. pneumoniae infection, which induces production of cytokines such as TNF-α, IL-1β and IL-6, and MMPs by macrophages. Furthermore, C. pneumoniae could lead to elevation of CRP and contribute to instability or progression of atherosclerotic plaques. The bacterium replicates in endothelial and smooth muscle cells and macrophages, and it can activate CD4+ and CD8+ T lymphocytes. *C.pneumonia* initiates inflammatory activation via the NF-κB pathway, resulting in increased expression of vascular cell adhesion molecule-1, enhanced recruitment of inflammatory leukocytes to the vessel wall, impaired activity of endothelial nitric oxide, increased platelet adhesion to endothelial cells and procoagulant activity in endothelial cells, as well as causing oxidation of LDL-C. Therefore, chronic infection may contribute to the risk of CHD by initiating a high level of immunologic activity, by raising triglyceride levels and decreasing HDL levels, and by increasing the concentrations of acute-phase reactants such as fibrinogen, CRP, and sialic acid [32 , 33].

3.6 Heart diseases, inflammatory diseases

In vivo sites of chlamydial infection demonstrate chronic inflammation characterized by activated monocytes and macrophages. Immunopathogenesis resulting from inflammation is the hallmark for chlamydia-induced disease. Chlamydial infection may elicit the inflammatory response via up-regulated cytokine production in infected or neighboring cells. Ingredients for this elicitation can include direct infection, lipopolysaccharide stimulation (LPS found on the outer surface of *C. pneumoniae*), and/or production of heat shock proteins, such as Hsp60. Proinflammatory cytokines (IL-1, TNF, IL-6) and TH1-associated cytokines such as IFN and IL-12 have been identified at sites of chlamydial infection[49, 50, 68].

Chlamydia infections are epidemiologically linked to human heart disease. A peptide from the murine heart muscle-specific alpha myosin heavy chain that has sequence homology to the 60-kilodalton cysteine-rich outer membrane proteins of *C. pneumoniae, C. psittaci*, and *C. trachomatis* was shown to induce autoimmune inflammatory heart disease in mice [6, 54]. Injection of the homologous Chlamydia peptides into mice also induced perivascular inflammation, fibrotic changes, and blood vessel occlusion in the heart, as well as triggering T and B cell reactivity to the homologous endogenous heart muscle-specific peptide [6, 54]. Chlamydia DNA functioned as an adjuvant in the triggering of peptide-induced inflammatory heart disease. Infection with *C. trachomatis* led to the production of autoantibodies to heart muscle-specific epitopes [6, 54]. Thus, Chlamydia-mediated heart disease is induced by antigenic mimicry of a heart muscle-specific protein [12].

Heart disease is the most prevalent cause of morbidity and mortality in rich countries. Numerous clinical and experimental studies suggest that chronic stages of heart diseases are, at least in part, mediated by autoimmune responses to cardiac antigens [54]. Inflammatory heart disease is caused by a wide variety of pathogens such as viruses, bacteria, and protozoa [54,68]. RNA of the picornavirus Coxsackie B3 (CVB3) is detected in the heart muscle of 40%–50% of patients with dilated cardiomyopathy (DCM), which is defined by enlargement of cardiac chambers, thinning of ventricular walls, and reduced

myofibrillar contractility [71]. Several bacterial infections (e.g., with Chlamydia species in particular) are also epidemiologically linked to human heart disease [6, 12, 24].

Because both Coxsackie virus and chlamydial infections are so common in humans, the identification of subsets of patients at risk of progression from acute infections to chronic cardiomyopathy is a large mystery. For example, who would do heart muscle biopsies in a patient with a common cold? Therefore, the challenge will be to identify both genetic and environmental factors that determine the progression to chronic heart disease and the development of DCM. Since autoinflammatory heart disease in humans can be reproduced in mice by immunization with heart muscle myosin, this experimental system has been used to analyze the immune response and host susceptibility.

Infections with bacteria that carry peptides that mimic endogenous heart-specific and heart-pathogenic epitopes lead to activation of autoaggressive lymphocytes. Pathogen-derived DNA contributes to immunactivation. The systemic effects of cytokines allow presentation of short cardiac myosin heavy chain (α-isoform) peptides in association with MHC class II molecules and the up-regulation of adhesion and homing receptors on APC resident within the target organ. The TNF-Rp55 appears to be a crucial receptor that controls target organ susceptibility in autoimmune heart disease via up-regulation of MHC class II on heart interstitial cells. After initiation of the inflammatory process by CD4^{+} T cells, CD8^{+} cells and macrophages are recruited into the heart muscle and contribute to disease pathogenesis. In addition, activation of B cells and production of auto antibodies may be involved in the progression of heart disease. This molecular scenario of autoimmunity also suggests that induction of disease depends on a fine balance between activation of self-reactive T cells and target organ susceptibility. The challenge for the development of successful prevention and treatment strategies will be to diagnose those few at risk of developing severe heart disease among the many with chlamydial or Coxsackie virus infections [6,12,54] .

3.7 Juvenile idiopathic arthritis

Infectious agents have been implicated in the pathogenesis of many rheumatologic diseases. In most of these diseases, including those in which specific organisms are known to play a role, the details of pathogenesis remain incompletely defined. Recent studies have aimed to isolate bacterial and viral pathogens from patients with rheumatic diseases, efforts have been made to further define the host immune response to infection, and there have been attempts to develop improved methods of diagnosis and treatment of infectious diseases affecting the musculoskeletal system.

Juvenile idiopathic arthritis (JIA) is a disease that was prominent with increased inflammation response in immune system, appeared mostly with peripheral arthritis. Endogenous and exogenous antigens play a role in the pathogenesis of disease. Two major reasons were thinking to be considerably important. First of them is immunological predisposition and the second one is environmental factors. Infections are considered to be the most important between environmental factors but also stress and trauma are also important in the etiology of the disease. However, the relation between JIA and infections is not clearly defined but the relation between adult chronic arthritis and infections was well-defined [1, 2].

Some investigators have suggested that *C.pneumonia* infection may be associated with atherosclerotic cardiovascular disease, asthma, multiple sclerosis and rheumatoid arthritis that is characterized by chronic inflammation of the synovium. Although *C.pneumonia* has been known to trigger a strong inflammatory response, there is no evidence to indicate a relationship between inflammation of the synovium and *C.pneumonia* [1, 5]. It is also not clear whether this micro-organism can trigger or exacerbate erosive joint damage. Taylor-Robinson *et al* investigated the relationship between JIA and *C.pneumonia* and suggested that larger studies with control groups were needed for more conclusive results [64].

The relationships between chronic synovitis and different bacteria, including mycobacteria, and viruses have been extensively studied by several investigators [1, 35]. Recently, detection methods for genetic material originating from micro-organisms in joint fluids have become readily available. Thus, a hypothesis stating that chronic synovitis is an immunological response to bacterial toxins has become more popular [30, 63].

Villareal focused on the role of *C.pneumonia*, which has a high prevalence amongst the general population, in the pathogenesis of chronic arthritis [65]. It was shown that *C.pneumonia* and C. trachomatis can spread to other anatomical locations by dissemination and cause chronic infections. Hannu evaluated 35 adults with reactive arthritis and demonstrated positive serology for *C.pneumonia* infection in four patients. These investigators also demonstrated that three patients had recently recovered from a lower respiratory tract disease [30]. With these findings, the authors reported that the reactive arthritis of these patients had been triggered by *C.pneumonia*, which could therefore be one of the triggering agents in the etiology of reactive arthritis [30, 64].

Taylor-Robinson *et al* investigated the relationship between JIA and C. pneumoniae in 19 children with JIA and showed that, *C.pneumonia* IgG antibodies were determinable in ten patients, but *C.pneumonia* DNA was found in only one child [64]. The presence of very high antibody titres in synovial fluids from this patient, along with another child with negative results for *C.pneumonia* DNA, suggested that the antibody may have been produced in the synovium [64].

It has been reported that C. pneumoniae can evoke a local inflammatory response when it is carried to the joint fluid. Gerard and Schumacher evaluated 212 patients with arthritis and reported C. pneumoniae DNA was present in synovial tissues of 13 % patients, but it was found in synovial fluids of only 4 % controls [25].

Wilkinson found C. trachomatis DNA in rheumatoid arthritis patients and in nearly one-third of unselected patients with undifferentiated oligoarthritis, which further supports the hypothesis that it plays an important role in disease pathogenesis. However, its presence did not correlate with evidence of an antichlamydial immune response. Despite previous anecdotal reports, C. pneumoniae does not appear to be a major cause of undifferentiated oligoarthritis or rheumatoid arthritis [69].

3.8 Diabetes

Obesity-associated chronic diseases, such as type 2 diabetes and atherosclerosis, are driven by inflammatory mediators, such as tumour necrosis factor-a (TNF-α) [71], which are also

expressed during infection. Epidemiological and pathological evidence has long linked highly prevalent chronic pathogens (i.e., *Chlamydia pneumoniae, Helicobacter pylori, Porphyromonas gingivalis*, hepatitis C virus, human immunodeficiency virus, influenza virus, cytomegalovirus, and herpes simplex virus type 1) to metabolic syndrome, insulin resistance type 2 diabetes, and coronary artery disease. *C.pneumonia* infection occurs with high frequency in virtually all humans during their lifetime, and numerous studies have demonstrated strong links between *C.pneumonia* infection and metabolic syndrome, insulin resistance, and coronary artery disease [46]. However, the cause and relationship has remained inconclusive, and the link was not confirmed in some studies or disappeared after controlling for body weight [17, 22]. Moreover, preventive antibiotic treatment failed to reduce the prevalence of secondary coronary events in large clinical trials, including a 4012-patient trial that tested a 1-year course of weekly azithromycin administration [29, 44- 46].

Murine *C.pneumonia* infection enhanced insulin resistance development in a genetically and nutritionally restricted manner via circulating mediators. The relevance for the current human diabetes epidemic remains to be determined, but this finding is potentially important because of the high prevalence of human *C.pneumonia* infection worldwide.

Fernández *et al* investigated the relationship between *C. pneumoniae* infection and peripheral arterial occlusive disease (PAOD) by analyzing clinical samples from 95 patients with PAD and 100 controls [22]. They did not find significant differences in anti-LPS IgG, anti-LPS IgA and anti-EB IgA between cases and controls but C. *pneumoniae* DNA findings in the vascular wall biopsy showed significant differences between cases and controls. This study showed significantly relationship between C. *pneumoniae* infection with PAD through the detection of anti-EB IgG from serum and bacterial DNA from arterial biopsy [22]. Study of Gutiérrez *et al* also showed that PAOD is significantly associated with *C. pneumoniae* infection through the detection of anti-EB IgG from serum and bacterial DNA from arterial biopsy [29].

3.9 Uveitis

The most common form of uveitis is anterior uveitis, which involves inflammation in the front part of the eye. It is often called iritis because it is usually only effects the iris, the colored part of the eye. The inflammation may be associated with autoimmune diseases, but most cases occur in healthy people. The disorder may affect only one eye. It is most common in young and middle-aged people. Posterior uveitis affects the back part of the uvea, and involves primarily the choroid, a layer of blood vessels and connective tissue in the middle part of the eye. This type of uveitis is called choroiditis. If the retina is also involved it is called chorioretinitis. Anterior uveitis is the most common form, and occurs annually at a frequency of about 8 to 15 cases per 100,000 people. This type of uveitis affects men and women equally. [34, 48].

Numazaki K *et al* found that the prevalence of serum IgA and IgM antibodies to *C. pneumoniae* in patients with endogenous uveitis associated with sarcoidosis was significantly higher than that in patients with other endogenous uveitis [48]. Huhtinen *et al* investigated the prevalence of antibodies to *C. pneumoniae* Hsp60 in patients with acute anterior uveitis

[34]. They did not find significantly difference in frequency and the level of IgG antibodies to *C. pneumoniae* Hsp60 between the patients and control subjects but the levels of IgA antibodies to *C. pneumoniae* Hsp60 were significantly higher in the patients than in the control subjects [48].

4. Conclusion

Immunological studies performed in animal models of autoimmune diseases strongly suggest that infections represent the best candidates for the environmental factors triggering human autoimmune disease. Only limited data are available as yet which show strong indications in this direction. However, the bulk of indirect evidence is serological data and important role of interferon-a in a number of autoimmune diseases, argue in favor of an etiological role for infections. More recently, *C.pneumonia* has been linked to a number of chronic human diseases and many autoimmune diseases with involving chronic inflammation and demyelination. The possible mechanisms of *C.pneumonia* involvement as aetiological agents or in the exacerbation of these diseases have been investigated intensively. Two basic elements are the association between bacterial infection and autoimmune disease and the involvement of the immune system in the disease process. We hope that the numerous studies in progress will provide the possibility of identifying the role of *C.pneumonia* in related autoimmune diseases. This would be important for the understanding of disease pathogenesis. It might prove of crucial clinical interest by opening up major therapeutic perspectives including anti-infectious agents, chemicals and monoclonal antibodies and vaccination.

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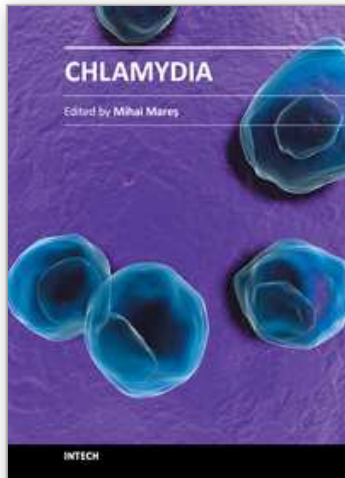
Chlamydia

Edited by Prof. Mihai Mares

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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