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Chlamydial Infections of the Heart

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Chlamydiae are common human pathogens, causing a broad spectrum of infectious diseases. Chlamydial infections involving the heart have been described in numerous previous reports. These organisms are documented to cause endocarditis, myocarditis and pericarditis. Furthermore, *Chlamydia pneumoniae,* the recently discovered respiratory pathogen, has also been implicated in coronary artery disease. For the first time the literature on involvement of the heart in chlamydial infections is reviewed. Information on the discovery of *Chlamydia* species is also included and the problem of the species determination of *Chlamydia* in interpretation of the older literature is mentioned.

The chlamydiae are members of a genus of obligate, intracellular, gram-negative bacteria which are distinguished from all other bacteria by a unique growth cycle. They are placed in their own order *Chlamydiales,* in the family *Chlamydiaceai,* with a single genus *Chlamydia* (1). Until recently the genus *Chlamydia* was recognised to contain two species, *Chlamydia psittaci* and *Chlamydia trachomatis. Chlamydia psittaci* is widely distributed in nature, causing genital, conjunctival, intestinal and respiratory infections in many mammalian and avian species (2). Psittacosis was first described in Switzerland by Ritter in 1879, who described several cases of unusual pneumonia associated with exposure to tropical birds. Morange in Paris, investigated an outbreak in 1894 and concluded that the parrots were the source of infection (3). The pandemic of 1929–1930 brought worldwide attention to the disease because of the high fatality rates of approximately 20 % seen in the preantibiotic era (4). Bedson isolated the filtrable agent from human and avian tissues in 1930 while investigating an epidemic at the London Zoo (3).

Human psittacosis is a zoonosis, usually contracted from exposure to an infected avian species. Psittacine birds are considered to be the major reservoir, but human cases have been associated with canaries, pigeons, sparrows, ducks, cockatiels and many other birds (1, 3). Close or prolonged contact with birds is not necessary for the acquisition of infection. Indeed, cases have been described where the patient contact with an infected bird, or with an environment in which an infected bird had been present previously, was only momentary (3). *Chlamydia psittaci* is also common in domestic mammals. Although human chlamydial infections resulting from exposure to infected domestic mammals are known to occur (5–7), they seem to be relatively uncommon. Human-to-human transmission has also been described, however such transmission is rare and is said to result in more severe disease (3).

Chlamydia trachomatis is exclusively a human pathogen. Intracytoplasmic inclusions characteristic of *Chlamydia trachomatis* infections were described for the first time in 1909 and in 1910 epithelial inclusions were found in the cervix of the mother of an infant with typical inclusion conjunctivitis (8). *Chlamydia trachomatis* was not isolated until 1957, when Chinese workers recovered the organism by inoculating conjunctival scrapings from trachoma patients into the yolk sac of embryonated hens' eggs (9). Improved laboratory methods, particularly tissue culture isolation techniques, were introduced in 1965 (10), and the microimmunofluorescent method for detection of antibodies to *Chlamydia trachomatis* and for immunotyping was introduced in 1970 (11).

This organism has been implicated as an etiologic agent in an increasing number of human diseases. The trachoma biotype strains (immunotypes A-K) cause trachoma and a wide range of sexually transmitted diseases (1, 2, 12, 13), and the LGV biotype strains cause lymphogranuloma venereum (1, 2). Other infections in adults

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reported to be caused by *Chlamydia trachomatis*, albeit rarely, are meningoencephalitis (14) and pneumonitis (15, 16). However, most of the evidence associating *Chlamydia trachomatis* with adult pneumonitis was based on serological tests and it is now thought that these were measuring cross-reacting antibodies to *Chlamydia pneumoniae* (17, 18). The organism is the leading cause of neonatal conjunctivitis (19). Approximately 60 % of infants exposed to *Chlamydia trachomatis* during birth contract the infection (20). Approximately one in three exposed infants develops conjunctivitis, and one in six develops pneumonia (1). *Chlamydia* pneumonia probably reflects descending infection, and bronchiolitis can also occur (1, 21).

A third species of *Chlamydia, Chlamydia pneumoniae* (TWAR), was identified recently (22). Studies have shown that the organism differs in a number of respects from *Chlamydia trachomatis* and *Chlamydia psittaci* (23–28). TWAR is a strain name derived from the laboratory designation of the first two isolates TW-183 and AR-39 (22). Since then, several strains of *Chlamydia pneumoniae* showing antigenic variation have been identified (18). Laboratory diagnosis is based on isolation of the organism and serological findings, and all evidence suggests that TWAR is a primary human pathogen that is transmitted from human to human without a bird or animal reservoir (29, 30).

Evidence that *Chlamydia pneumoniae* is responsible for a significant proportion of respiratory tract infections has been accumulating over the last few years. Isolation of the TWAR organism and serologic evidence of recent *Chlamydia pneumoniae* infection has most commonly been found in patients with pneumonia (31). However, the organism has also been associated with bronchitis, pharyngitis and sinusitis (28, 30, 31). *Chlamydia pneumoniae* infection may be either a first infection or a reinfection. A febrile illness without local signs has been also associated with *Chlamydia pneumoniae* infection (22). The results of the microimmunofluorescence test to detect antibody are accepted as indicating *Chlamydia pneumoniae* infection (28, 30, 31).

The prevalence of antibodies to *Chlamydia pneumoniae* increases with age, and is about 50 % in middle-aged adults through the world (20). Estimates from antibody prevalence data indicate that every person will experience at least one *Chlamydia pneumoniae* infection during his lifetime (22, 32), and that reinfection with *Chlamydia pneumoniae* is common.

Chlamydial infections involving the heart have been described in numerous previous reports. Although many of these reports are circumstantial, findings in several recent studies provide evidence of this association. These organisms may cause endocarditis, myocarditis and pericarditis. Furthermore, *Chlamydia pneumoniae* may also be associated with coronary artery disease.

We review for the first time the literature dealing with cardiac involvement associated with chlamydial infections. However, in older studies the species determination for *Chlamydia* is imprecise (1, 8, 17, 18, 33, 34). Although it is now recognised that the complement fixation test measures antibodies common to all chlamydial species (3, 8, 29, 31) as all these species have a common genus-specific group antigen, which is the basis of the complement fixation test, in older studies this test was used in the belief that it measured only antibodies to *Chlamydia psittaci*. Likewise, a positive Frei test, a skin test performed with tissue culture antigen injected intracutaneously and read in much in the same manner as a tuberculin test, was interpreted to indicate lymphogranuloma venereum (35). Nowadays this test is known to measure mainly hypersensitivity to the lipopolysaccharide antigen common to all three chlamydial species, and does thus not distinguish the causative chlamydial species (8). Similarly, the inclusion immunoperoxidase and immunofluorescence tests measure cross-reacting antibodies and do not reliably differentiate between the three chlamydial species (1, 3, 8, 31).

Chlamydiae and Endocarditis

It is well recognised that *Chlamydia psittaci* is a pathogen in cardiovascular disease, numerous reports indicating that in addition to endocarditis it may also cause myocarditis and pericarditis (6, 36–55). These reports emphasise that *Chlamydia psittaci* should be recognised as a cause of infective endocarditis (6, 36, 48–61). In such cases serological tests to detect *Chlamydia psittaci* should be performed, especially in the presence of negative blood cultures. Most patients reported contact with birds, budgerigars, parrots, canaries and pigeons being implicated as the main sources of infection (54). In such cases it should be demonstrated that the bird is actually the vec-

tor as other animals, including the domestic cat, can also spread the disease (6, 54).

Generally, the infection affects previously abnormal valves, although involvement of previously normal valves has also been reported (36, 50, 58, 60). Infective endocarditis due to *Chlamydia psittaci* may be severe. As in other chlamydial infections, the clinical course may be acute, subacute or indolent (6, 49, 50). The aortic valve was involved in most cases (6, 36, 50, 54, 55, 57,59). The mortality rate was high (50, 54, 55), and in many cases valve replacement was needed (36, 49, 50, 54).

Chlamydia trachomatis should also be added to the list of organisms that may cause infective endocarditis with negative blood cultures. As with *Chlamydia psittaci*, *Chlamydia trachomatis* infections can involve one or more heart valves in patients with previously normal or abnormal valves (62–65). In addition, a case of endocarditis associated with *Chlamydia trachomatis* in a patient with a congenital ventricular septal defect and no evidence of valvular disease has also been reported (66). Although as yet only a few cases of *Chlamydia trachomatis* endocarditis have been reported, since *Chlamydia trachomatis* genital infections are widespread it is conceivable that many cases of *Chlamydia trachomatis* endocarditis remain undiagnosed, and that the scarcity of reported cases is due to lack of awareness of its occurrence. The outcome may be fatal (62), however treatment with antimicrobial agents is usually effective. In addition to *Neisseria gonorrhoeae* (67), *Chlamydia trachomatis* must be considered as an organism causing venereal disease which is potentially capable of causing infective endocarditis involving also normal heart valves (62).

Despite its recent discovery, *Chlamydia pneumoniae* has already been implicated in several cases of endocarditis (22, 29, 68–70). In some of these cases pneumonia was the primary infection (29, 68). The aortic valve was involved in the majority of endocarditis cases. Since infection with *Chlamydia pneumoniae* is much more common than infection with other *Chlamydia* species, and since reinfection is frequent (29), it is possible that many cases of *Chlamydia pneumoniae* endocarditis remain undiagnosed. Increased recognition of this newly discovered microorganism may yield more reports of endocarditis associated with *Chlamydia pneumoniae* infections.

Chlamydiae and Myocarditis

Acute myocarditis may arise during or after a great number of infectious diseases. Previously, beta-haemolytic streptococci dominated as the causative agent (71), while today coxsackie B viruses are considered to be the most common cause (72). Electrocardiographic and epidemiologic studies indicate that myocarditis occurs in 5–15 % of patients with common infectious diseases (73, 74), in most cases without clinical signs or symptoms. The infective agent has to be isolated from the myocardium or from the pericardium in myocarditis in order to fulfill the criteria for a high degree of association. Since in many cases myocarditis is a postinfectious manifestation, it is often only possible to demonstrate a significant increase in the antibody titre for a suspected agent, which gives a low degree of association (75). However, in some cases a constant high antibody titre is the only clue to the possible etiology of myocarditis (75).

There are numerous previous reports implicating *Chlamydia psittaci* as a causative agent of myocarditis (33, 34, 37–40, 43–48, 53, 76–81). Some of these cases had a fatal outcome (78). In 1930 Adamy (82) commented for the first time on the development of postinfectious myocardial degeneration associated with psittacosis. Subsequently, psittacosis infection has been implicated in myocardial disease in reports from several countries (37, 43–48). Grist and McLean (48) found enlargement and failure of the heart to be a recognised feature of psittacosis. The primary infection in psittacosis myocarditis appears to be pulmonary (37, 83).

There are only eight reported cases of myocarditis associated with *Chlamydia trachomatis* infection, six of which occurred in children and infants (83–85), two with a fatal outcome. One adult with *Chlamydia trachomatis* myocarditis presented with cardiogenic shock in which the myocarditis resembled a large anterior myocardial infarction. Only after detailed invasive evaluation was the diagnosis of myocarditis established, and five months later clinical cure was achieved (86). We recently described another case in an adult in which the myocarditis led to chronic dilated cardiomyopathy, a complication which has not been reported previously in association with *Chlamydia trachomatis* infection (87). The patient later died of intractable heart failure.

Only a few cases of myocarditis have been associated with *Chlamydia pneumoniae* infection

(22, 29, 68,88). In some of these cases pneumonia was the primary infection (29, 68). However, as mentioned with endocarditis, since *Chlamydia pneumoniae* is a newly discovered microorganism and infections with *Chlamydia pneumoniae* are more common than with the other *Chlamydia* species, it is possible that many cases of *Chlamydia pneumoniae* myocarditis remained undiagnosed, and that increased recognition of this bacterium may yield more reports of *Chlamydia pneumoniae* myocarditis.

Idiopathic dilated cardiomyopathy is an increasingly common disorder, with an estimated annual incidence of 7.5 cases per 100,000 persons (89). Approximately 10,000 persons in the USA die of the disease each year (90), and the mortality rate in patients with the disorder is approximately 20 % per year (91). This mortality rate is substantially higher than that in patients who have had myocardial infarctions (92). Several studies show that active myocarditis is capable of producing acute dilated cardiomyopathy (93–96), and that some of the acute cases evolve into a chronic form of dilated cardiomyopathy that would otherwise be labelled idiopathic (97–102). It can thus be concluded that many cases of unexplained dilated cardiomyopathy result from myocarditis.

The majority of episodes of myocarditis are probably subclinical, and a substantial portion of myocarditis cases are of unknown etiology. As chlamydiae are relatively common infectious agents, and as the myocardium is one of its target organs, it might be that many cases of myocarditis related to non-specific viral syndromes without appropriate diagnostic tests or of unknown etiology were due to chlamydial infection. Thus chlamydiae should be considered in cases of myocarditis where no other cause can be decisively demonstrated. Since there is usually no specific therapy for patients with myocarditis and the prognosis is often grave, diagnosis of possible infection with chlamydiae, which usually responds to antimicrobial therapy, is of great importance. Efforts to explore further the etiologic role of chlamydiae in myocarditis should include, in addition to serological tests, efforts to isolate the organism from the nasopharynx, cervix and rectum of patients, and blood and urine cultures. In addition, there are now several new techniques available that can directly detect the organism in heart tissue, such as immunocytochemistry, in situ hybridization and polymerase chain reaction (103–108).

Chlamydiae and Pericarditis

Chlamydia psittaci may also involve the pericardium causing pericarditis. Several cases have been reported (33, 37, 53, 78, 109–114), sometimes in association with myocarditis (33, 37, 78). In some cases the pericarditis was accompanied with pericardial effusion (37, 109, 111). In one case a large pericardial effusion developed and required pericardiocentesis (109). In cases with pericardial effusion after *Chlamydia psittaci* infection the response to standard antibiotic therapy was slow which may reflect difficulty in eradicating the organism from the pericardial effusion (109). Sulton et al. (37), in a review of 599 unselected cases of acute pericarditis, found nine cases with serological evidence of psittacosis with pericardial effusion in two. In four cases heart disease was the only clinical manifestation. Five patients recovered completely but their treatment regimens were not reported.

Measurement of antibody titres for *Chlamydia psittaci* is recommended in all cases of acute pericarditis regardless of pulmonary involvement. If the diagnosis is confirmed, treatment with oxytetracycline should be continued for at least two months (109).

Until now no cases of pericarditis caused by *Chlamydia trachomatis* or *Chlamydia pneumoniae* have been reported. However, as these two microorganisms may involve the endocardium and the myocardium, we believe that these two *Chlamydia* species could also involve the pericardium, and that the absence of reported cases is due to lack of awareness of its occurrence.

Chlamydiae and Coronary Heart Disease

Until now there have been only two reports of a possible association between *Chlamydia psittaci* infection and myocardial infarction (59, 76), and there are no reports associating coronary heart disease with *Chlamydia trachomatis*.

Regarding *Chlamydia pneumoniae,* Saikku et al. (115) recently demonstrated a strong association between *Chlamydia pneumoniae* and both chronic coronary heart disease and acute myocardial infarction. The study was carried out in Finland, where, as in other Scandinavian countries, *Chlamydia pneumoniae* causes widespread epidemics every four to five years (29, 116, 117). Paired sera from 40 male patients with acute

myocardial infarction, 30 male patients with chronic coronary heart disease, and 41 controls were investigated for antibodies to *Chlamydia pneumoniae*. Twenty-seven patients with acute myocardial infarction and 15 patients with chronic coronary heart disease had raised IgG and/or IgA titres in a microimmunofluorescence test with *Chlamydia pneumoniae*. In both groups the frequency was significantly higher than in the controls. In view of these findings they suggested that a possible relationship between *Chlamydia pneumoniae* infection and acute myocardial infarction and chronic coronary heart disease should be considered in studies of possible pathogenic mechanisms and the epidemiology of coronary heart disease. In another recent study Leinonen et al. (118) demonstrated elevated chlamydial lipopolysaccharide-containing immune complexes in the sera of 57 % of patients with acute myocardial infarction compared with 12 % of controls. These findings provide further evidence of a possible association between chronic *Chlamydia pneumoniae* infection and acute myocardial infarction. A recent study in the USA has confirmed the above preliminary findings, showing an association between elevated *Chlamydia pneumoniae* titres and angiographically verified coronary heart disease (119). Additional evidence of a possible association between *Chlamydia pneumoniae* infection and coronary heart disease has recently been provided by two other case-control studies. One was a large-scale prospective study on the incidence of coronary heart disease by Saikku et al. (32) using data from the Helsinki Heart Study, and the other a US study by Thom et al. (120).

The findings of the above studies are thus strongly supported of an infectious etiology in the development of coronary heart disease and acute myocardial infarction (121–126).

Conclusions

Chlamydiae are common human pathogens, causing a broad spectrum of diseases. Human psittacosis, although long recognised, is probably the least important human chlamydial disease. Chlamydial infections may involve the heart, causing endocarditis, myocarditis and pericarditis. Furthermore, *Chlamydia pneumoniae* may also cause coronary artery disease. Infection with all three *Chlamydia* species is usually responsive to treatment with tetracycline and erythromycin. Efforts to explore further the etiologic role of *Chlamydia* species in heart disease should include, in addition to serological tests, efforts to isolate the organism from the nasopharynx, cervix and rectum of patients, and blood and urine cultures. Furthermore, in cases of myocarditis or pericarditis efforts should be made also to isolate the infective agent from the myocardium or the pericardium. For this purpose newly available techniques that directly detect the *Chlamydia* organism in heart tissue, such as immunocytochemistry, in situ hybridization and the polymerase chain reaction may be helpful.

A possible relationship between *Chlamydia pneumoniae* infection and coronary heart disease could have important implications since the infection is common and there might be potential for reducing the incidence of coronary heart disease as the organism usually responds well to antimicrobial therapy. As definitive microbiological evidence of a causal relationship between *Chlamydia pneumoniae* infection and coronary heart disease is still lacking, recent findings should serve to stimulate additional studies in search of such evidence.

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