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INFECTION AND ARTHRITIS (K WINTHROP, SECTION EDITOR)

Chlamydia-Induced Reactive Arthritis: Disappearing Entity or Lack of Research?

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Abstract

Purpose of Review Recent studies regarding the frequency of *Chlamydia*-induced reactive arthritis (ReA) are reviewed, with a focus on the question of whether the entity is in fact disappearing or whether it is simply being underdiagnosed/underreported. Epidemiological reports indicate diversity in the frequency of *Chlamydia*-associated ReA in various parts of the world, with evidence of declining incidence in some regions.

Recent Findings The hypothesis that early effective treatment with antibiotics prevents the manifestation of *Chlamydia*-associated ReA requires further investigation.

Summary For clinicians, it is important to remember that ReA secondary to *Lymphogranuloma venereum* (LGV) serovars L1–L3 of *C. trachomatis* is probably underestimated due to a limited awareness of this condition, the re-emergence in Western countries of LGV overall, and the present increasingly rare classical inguinal presentation.

Keywords Reactive arthritis · *Chlamydia trachomatis* · *Chlamydia pneumoniae* · Epidemiology · *Lymphogranuloma venereum*

Introduction

Infections caused by the urogenital pathogen *Chlamydia trachomatis* (*C.tr.*), a leading cause of bacterial sexually transmitted infections, and the related species *Chlamydia pneumoniae* (*C.pn.*), responsible for respiratory tract infections including pneumonia, pharyngitis, and bronchitis, can and do generate reactive arthritis (ReA) and spondyloarthritis (SpA) [1••, 2••]. In recent years, the frequency of diagnosis, and basic research and clinical studies related to *Chlamydia*-induced ReA and SpA have declined significantly. This engenders the question of whether the entity actually is disappearing or whether simply little or no current research interest exists. *Chlamydia*-induced ReA is part of sexually acquired ReA (SARA), which also may be caused by other microorganisms, including *Mycoplasma genitalium* and *Ureaplasma urealyticum* (reviewed in [3]). ReA also can be elicited by gastrointestinal infections, for example, infection by *Clostridium difficile*, various species of *Salmonella*, and others (e.g., [4, 5]).

A recent review provided considerable anecdotal evidence that SARA is less frequent in the UK than it was a decade or more ago [6]. Moreover, an earlier report from an analysis of cases with *C.tr.*-induced ReA appearing in the Greek Army indicated that the incidence of this condition might be in decline in that context as well [7]. In this article, we discuss recent reviews and primary research reports with a focus on studies of the recognition and incidence of *Chlamydia*-induced ReA. We performed an extensive PubMed search using the keywords "*Chlamydia* reactive arthritis" and "*Chlamydia* spondyloarthritis," and from the resulting list, we selected all sensibly related and relevant publications from 2016 to 2018. Further, we discuss advances in our understanding of the pathology elicited by chlamydial infections, as well as diagnosis and perspectives in treatment, and we point out research areas that should provide useful new insights into the pathogenesis process in the joint.

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Basic Research and Pathology

C.tr. causes genital infections worldwide, and such primary chlamydial infections frequently cause severe sequelae, including inflammatory arthritis (e.g., [5, 6, 8, 9]). *C.pn.* is a related respiratory pathogen, and infections with this organism also have been linked to sequelae, including an inflammatory arthritis. Clinical aspects of *C.pn.*-induced arthritis mirror to some extent those of *C.tr.*-induced arthritis. The primary chlamydial host cell type is epithelial, but other cell types can be infected including monocytes, which serve as the vehicle by which the organisms disseminate to the joint (e.g., [10]). Importantly, and as developed in detail in other publications, chlamydiae of both species relevant to generation of ReA progress to an unusual metabolic state designated "persistence," which is critical to long-term residence in the synovium (reviewed in [1••, 11••]).

Recent studies have illuminated the means by which invading chlamydiae influence host cell processes, many of which are relevant to the genesis of ReA. For example, the gene designated CT622 on the genome *C.tr.* encodes a product which is injected into the host cytoplasm throughout the developmental cycle; loss of the encoded protein attenuates infectivity and intracellular development during the cycle [12]. Similarly, loss of the CT228 gene product significantly alters the duration of active host cell infection [13]. *C.tr.* modulates host cell glucose transport via upregulation of *GLUT1* and *GLUT3*, and that upregulation is dependent on chlamydial protein synthesis [14]. Chlamydiae require iron from the host, but we do not fully understand the mechanisms by which they accomplish acquisition [15•]. Other recent studies demonstrated the means by which chlamydial proteins influence host cell apoptosis (e.g., [16]). Another study identified dual Lys63-deubiquitinase and Lys-acetyltransferase activities in the *Chlamydia* protein ChlaDUB1; these lead to the breakup of the host cell Golgi apparatus [17]. All these manipulations of the host cell abet the ability of the pathogen to elicit joint disease. Reviews from a number of sources highlight these and other aspects of interaction with their immediate host cells by chlamydiae (e.g., [18•]).

Major issues that remain to be elucidated include (i) the timing of the extravasation of infected cells from the genital tract, (ii) whether some specific homing function draws the infected cells to the joint, (iii) whether some process operates that selects a particular serovar/strain of the pathogens for long-term residence in the joint, and (iv) various aspects of the molecular genetics of chlamydiae once they are resident in synovial tissue. Importantly, as yet unknown, attributes of the host genetic background also must influence dissemination of the organism to the joint, behavior of the pathogen in that context, and the route to chronicity in some individuals.

Epidemiology

Discussion of the epidemiology of *Chlamydia*-induced ReA is somewhat problematic because of the lack of specific diagnostic criteria, the variability of host genetic background including differing prevalence of human leukocyte antigen-B27, the local environmental factors, the variable disease course, the high frequency of asymptomatic preceding infections with *Chlamydia*, and most importantly several reports that incidence of the disease may have been declining for some time (e.g., [19]). Although a typical analysis of the epidemiology of a disease entity should include incidence and prevalence, the attack rate also is of significance [19]. That rate is the percentage of ill persons out of all persons reporting a risk behavior and thus is a variant of an incident rate, applied to a narrowly defined population observed for a limited period of time [20]. Estimated attack rates of ReA following chlamydial infection range from 1% to as high as 15%, but generally are around 5% [21].

Chlamydia is widely understood to be the most common infection causing sexually acquired ReA. For that reason, Denison et al. carried out the first systematic literature review to collate and critically evaluate the published evidence regarding the incidence of SARA, with the exception of sexually associated infection with the human immunodeficiency virus [22••]. All prospective studies in which ReA could be assessed at the time of diagnosis of infection or at follow-up were included. Only studies with laboratory confirmation of the infection were further analyzed to avoid biasing rates due to including subjects with infection based on self-report. After screening, three papers met all relevant inclusion criteria for the review. These papers were published over a 35-year period (1978, 1996, 2013), two in the USA and one in the UK [22••]. The studies reported an incidence of SARA of 3.0–8.1% and were found to be of low to moderate quality. Thus, a suggested screening tool with a questionnaire adapted for use in future studies of the incidence of SARA was included. It should be noted that all three studies reported attack rates in selected patients attending a sexually transmitted or communicable disease clinic and thus did not present a true assessment of population-based incidence [23–25]. A study which did investigate a population-based incidence of *C.tr.*-induced arthritis was not cited [26]. This prospective study reported an annual minimum incidence of 4.6/100,000 individuals primarily seen during a 2-year period (1988–1990) by general practitioners in a defined Norwegian community. In contrast, a prospective population-based incidence study (between 1999 and 2000) of new referrals, conducted to establish the annual incidence of inflammatory joint diseases in the adult population of 132,000 in the County of Kronoberg in Southern Sweden, identified only one patient with undifferentiated arthritis with *C.tr.* detected in urine at the 3-month visit, but not at inclusion [27]. An acute *C.pn.* infection preceded one case of ReA and one case of rheumatoid arthritis.

Mason and colleagues assessed trends and risk factors for ReA over the 20-year period 1992–2012 in a large urban sexual health clinic, the Sydney Sexual Health Centre [28••]. Cases must have been seen at least once during the retrospective case-control study period at that clinic, with a primary reason for their visit being identified and coded as ReA by the treating physician. Patient files were reviewed manually, and those with a history of two or more specific symptoms or signs of ReA were included, to allow for inclusion of milder presentations seen in a primary care setting. The rate of ReA diagnoses decreased over time (23 in 1992–1996 to one in 2007–2011 and none in 2012), while *Chlamydia* diagnoses increased (770 in 1992–1996 to 2257 in 2007–2011) [28••]. The strength of the study was the long time period of analysis; however, the small sample size, the retrospective study design, and the missing urine and/or blood and synovial PCR testing for *Chlamydia* are limitations. ReA was not associated with current or recent *Chlamydia* infection but was marginally associated with past non-gonococcal urethritis. The reason for this apparent disconnect between the decline in ReA diagnoses despite an increase in *Chlamydia* diagnoses is unknown. Antibiotic and early treatment of *Chlamydia* have been suggested to reduce the risk of developing ReA [28••].

Other recent studies have also addressed the issue of the frequency of *C.tr.*-induced ReA. *C.tr.* infection in urethral and cervical smears was found in 13.0% in patients with ReA (n = 323), compared with 2.4% in a control group of volunteers without urogenital or joint symptoms, in a study conducted in 2001–2012 within the area of the Podlaskie province (north eastern Poland) [29•]. A limitation of the study is that no population-based incidence rate was provided. Nevertheless, the data show a remarkable frequency of *C.tr.*-induced ReA in the area investigated in Poland. No correlations between detecting the presence of *C.tr.* in the urogenital tract and presence of specific IgA class antibodies in the serum of ReA patients were observed. The majority of patients with the presence of IgG antibodies and lack of IgA antibodies in the serum had longer than a 1-year history of joint symptoms.

A prospective study carried out from 2009 to 2016 assessed the prevalence of *Chlamydia*-associated ReA among patients with proved *C.tr.* genital infection, using standard PCR testing with urine samples, in patients attending an urban clinic of general practice and rheumatology in Tokyo [30••]. All patients with *C.tr.* genital infection were treated with 1 g of azithromycin in a single dose and evaluated for the abolition of infection 1–2 weeks after treatment, using nucleic acid amplification testing (PCR). Using a standardized questionnaire, the consecutively recruited adults with proven *C.tr.* genital infection were screened for symptoms of ReA. A follow-up questionnaire was administered at least 6 weeks later by telephone or through a revisit to the clinic. Patients who claimed at least one symptom of arthritis were evaluated by a rheumatologist for diagnosis of ReA. Only one patient out of the 123 patients enrolled in this study actually developed ReA. This patient was 31 years old and developed arthritis of the sacroiliac joints. The authors concluded that the prevalence of *Chlamydia*-associated ReA among patients with *C.tr.* genital infections is lower than reported previously. One of the reasons for this discrepancy was suspected to be the early effective treatment with antibiotics in this study.

Patients with a diagnosis of ReA hospitalized in a French rheumatology department were analyzed in a retrospective monocentric study to compare clinical and biological features, management, and outcome, between two periods: from January 1984 to December 1993, and from January 2004 to December 2013 [31••]. *C.tr.* ReA was the most frequent diagnosis, and no significant difference was identified between the two periods in the number of new cases with 33 and 31, respectively. The study confirms that *C.tr.* ReA is still present in a tertiary rheumatology unit in a developed country using clinical expertise and available diagnostic serological and molecular biology testing. Some limitations of the study are discussed in the report, e.g., the retrospective analysis, absence of universal classification criteria, and potential referral biases.

Taken together, recent studies indicate diversity in the frequency of *Chlamydia*-associated ReA in different parts of the world, with evidence of declining incidence in some regions. The hypothesis that early effective treatment with antibiotics prevents the manifestation of *Chlamydia*-associated ReA needs further investigation in a prospective placebo-controlled trial. Moreover, no epidemiological information is available for *C.pn.*-associated ReA and SpA, a causative entity of chlamydial infection described only in case studies as less frequent [32, 33]; however, approximately 50% of young adults and 75% of elderly persons have serologic evidence of a previous *C.pn.* infection [34].

Clinical Research

Serological analysis of chlamydial infections is still mainly based on micro-immunofluorescence and enzyme-linked immunosorbent assays (ELISA) with their known limitations of poor sensitivity and cross-reactivity. To overcome the limitations of conventional serology, a novel microarray was designed carrying 52 synthetic peptides representing B cell epitopes from immunodominant proteins of all 11 chlamydial species [35•]. The assay is capable of simultaneously identifying specific antibodies to each *Chlamydia* spp. and could demonstrate dual infection with *C.tr.* and *C.pn*. However, in many clinical situations, direct detection of the organism is the diagnostic strategy of choice. To accomplish such detection, a number of commercial molecular genetics-based assays are currently available and in standard use in clinical laboratories (e.g., the Becton-Dickenson Viper™ system targeting

Chlamydia and *Neisseria gonorrhoea*; also the Aptima Combo 2™ system from Hologic Diagnostics) (see, e.g., [36]). To a large extent, proper functioning of these systems is dependent on adequate template preparation prior to screening assays. Further, they do not all work equally well on all types of clinical specimens. Regardless, the availability of nucleic acid-based screening systems in the clinical laboratory will remain the standard for direct detection of chlamydiae in clinical samples.

In recent years, research on the rheumatologic manifestation of chlamydial infections has been limited to rare and underrepresented topics. For example, a few cases of reactive arthritis secondary to LGV serovars L1–L3 of *C.tr.* have been described, but they have been restricted to men who have sex with men (MSM) following an episode of proctitis [37•, 38]. Foschi et al. reported the first case of reactive arthritis associated with LGV in a human immunodeficiency virus-negative woman with urogenital and rectal *C.tr.* L2 serovar infection [37•]. The 50-year-old Italian woman presented with oligoarthritis of the left knee, both ankles, and a right metatarsophalangeal joint dactylitis with sausaging of the third right toe. Urine sample and the rectal swab screened positively for *C.tr.* DNA, and molecular genotyping based on the *omp1* gene semi-nested polymerase chain reaction followed by restriction fragment length polymorphism analysis identified a L2 serovar. Serological test for anti-chlamydial antibodies revealed a significant increase of *Chlamydia* IgG and IgA values. Interestingly, LGV urogenital localization was completely asymptomatic, whereas the symptoms of LGV rectal infection—anal pain, mucous-hematic anal discharge, and tenesmus, arising after unsafe receptive anal and vaginal intercourses with an occasional male partner—was initially misdiagnosed and confused for recurring internal hemorrhoids by the patient. Based on the final diagnosis of ReA secondary to LGV infection, antibiotic therapy with oral doxycycline 100 mg twice a day for 3 weeks was established. Three months after treatment at follow-up visit, the patient had completely recovered, and the test of cure was negative for LGV infection. Even if less frequent than the ReA related to *C.tr.* serovars D-K, LGV-associated arthritis may be a newly emerging manifestation of this disease; it is probably underestimated because of the low awareness of this condition, the re-emergence in Western countries of LGV overall, and the currently increasingly less common classical inguinal presentation [39, 40].

A rare manifestation of *C.pn.* infection is lower-leg cellulitis-like manifestations of erythema nodosum (EN) [41]. A 42-year-old Japanese man without significant medical history presented with a tender erythematous swollen right lower leg and recurrent episodes of erythematous oedema affecting both legs, associated with fatigue, fever, night sweats, arthritis, and myalgia. A skin biopsy demonstrated septal panniculitis with vasculitis, as well as infiltration of lymphocytes and neutrophils into the adipose septa and paraseptal blood vessel walls. Laboratory testing revealed an elevated anti-*C.pn.* IgM index of 2.12, suggesting an acute *C.pn.* infection. Treatment with minocycline hydrochloride 100 mg/day resolved the clinical problems within 10 days. Nevertheless, considering that approximately 60–70% of healthy individuals are seropositive for *C.pn.*, causality is questionable in this case, even though no other causes were found and antibiotic treatment proved to be successful.

The association of *C.pn.* with EN is rare. Analyses of five reported cases show the following clinical characteristics: comparatively young age (29.8 ± 13.2 years), atypical EN without tender nodules in two cases, high fever in 4 patients, myalgia in 3 patients, respiratory symptoms such as cough in 2 patients, and chest X-ray abnormal findings in 2 patients [41]. Laboratory examinations revealed a high erythrocyte sedimentation rate in 4 patients, whereas an elevated white blood count was observed in only one patient. All the patients improved with treatment using tetracyclines or macrolides.

Reports focusing on coinfections of chlamydiae and other bacteria in ReA and SpA have been rare. We recently reviewed the extant data regarding infections by chlamydiae and other pathogens in the joint as they relate to engendering arthritis, and we suggested a number of research areas that must be given a high priority if we are to understand this issue. Therefore, we urge clinicians to treat such arthritides in an effective manner [42••]. Interestingly, Wolford et al. reviewed current information regarding the role of *Chlamydia* in temporomandibular joint (TMJ) ReA and referred to an earlier PCR study of patients with TMJ ReA; that study reported positive PCR results for *C.tr.*in 43%, for *M. genitalium* in 35%, for *M. fermentans* in 23%, and for more than 1 species in 31%, of the patients included [43, 44]. Finally, a recent study investigated the presence of *C.pn.* in 75 patients with primary OA who underwent total knee arthroplasty [45]. Real-time PCR showed no evidence of the presence of *C.pn.* in the patients' synovial biopsy specimens and synovial fluid, nor were other bacteria detected.

Treatment

Parallel, randomized controlled trials were reviewed to assess the efficacy and safety of antibiotic treatment for *C.tr.* genital infection in men and non-pregnant women [46]. The authors concluded: "In men, regimens with azithromycin are probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure. For women, we are uncertain whether azithromycin compared to doxycycline increases the risk of microbiological failure. Azithromycin probably slightly reduces adverse events compared to doxycycline in men and women together but may have little difference in men alone." The impact of

these findings to the rheumatologist diagnosing symptomatic or asymptomatic infection is not straightforward. Should he prescribe in the future doxycycline instead of azithromycin to eradicate the persistent urogenital infection in man?

Carter and Hudson recently reviewed the present state of treatment for *Chlamydia*-induced ReA, together with the advances in basic research into the biology and host-pathogen interactions involved in the disease; they also discussed a promising approach to cure chronic post-chlamydial ReA, specifically with a prolonged course of combination antibiotics [47••]. However, available studies regarding this approach have involved only a small number of patients. Thus, a critically important current issue centers on confirmation of those initial data using larger patient cohorts, as well as additional antibiotic choices and combinations. Few other relevant such studies are available.

Lycopene, a main dietary carotenoid, was reported recently to be a possible alternative for antibacterial therapy against chlamydiae [48]. In in vitro studies, lycopene has demonstrated a strong inhibitory effect on *C.tr.* and *C.pn.* infections in alveolar macrophages. A single daily oral dose of 7 mg lycopene for 4 weeks was given in a pilot clinical study to 36 patients with cardiovascular disease and who were positive for IgG anti-*C.pn.* antibodies. That treatment reduced stepwise anti-chlamydial IgG antibodies to a level three-fold below baseline. Additional studies clearly are needed to further explore the anti-chlamydial activity of lycopene and its potential efficacy in treating *Chlamydia*-induced ReA.

Conclusions

The overall number of published primary research reports and reviews focused on *Chlamydia*-induced ReA and SpA has declined significantly in recent years. As indicated above, we did an extensive PubMed search using the keywords "*Chlamydia* reactive arthritis" and "*Chlamydia* spondyloarthritis"; that search indicated that from 2010 to 2018, a noticeable decline in publications obtained: 2010–2012, 37 publications; 2013–2015, 30 publications; and 2016–2018, 20 publications. The reason(s) for this paucity is/are unclear at this point. While it is possible that the explanation lies in attenuated clinical and research interest for some reason in this condition, this seems an unlikely explanation. In contrast, some investigators have argued that the condition actually is disappearing because of increased early and effective antibiotic treatment of the inciting primary genital chlamydial infection. Certainly, epidemiological studies have indicated a diversity of the incidence and frequency of *Chlamydia*-associated ReA in different parts of the world, with evidence of declining incidence in some regions. In our view, however, the hypothesis that such early treatment has severely attenuated, or even eliminated, the number of new cases of *Chlamydia*-associated ReA requires further investigation. Moreover, when thinking about this disease, the default view so to speak focuses on prior genital infection with *C.tr.* An important current issue, though, concerns the epidemiology and clinical details relating to *C.pn.* infections as the etiologic agent eliciting ReA and SpA. Similarly, LGV-associated arthritis is certainly underreported due to the current low level of awareness of this condition, the re-emergence in Western countries of LGV overall, and the increasingly rare classical inguinal presentation. Thus, we argue that *Chlamydia*-induced joint disease should, indeed must, remain an area for productive research, and we urge both basic science and clinician investigators to refocus attention on it over the next several years.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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