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Chlamydiae as Etiologic Agents for Chronic Undifferentiated Spondyloarthritis

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Abstract

Objective—The majority of cases of *Chlamydia*-Induced reactive arthritis (CiReA) do not present with the classic triad of arthritis, conjunctivitis/iritis, and urethritis. Moreover, acute chlamydial infections are often asymptomatic. The aim of the present study was to assess the prevalence of synovial *C. trachomatis* (Ct) and *C. pneumoniae* (Cpn) infections in subjects with chronic undifferentiated spondyloarthritis (uSpA).

Methods—Study subjects met the European Spondyloarthropathy Study Group (ESSG) criteria without evidence of ankylosing spondylitis, psoriasis, inflammatory bowel disease, or preceding dysentery. Symptoms were present for at least 6 months. Data collected on the day of the test included standard demographics, history and physical examination (including joint count, evaluation for dactylitis and/or enthesitis, and skin exam), HLA-B27, history of Ct or Cpn. Each subject underwent synovial biopsy; tissue and concomitantly procured PBMC were analyzed by PCR for Ct and Cpn DNA. Synovial tissue from 167 subjects with osteoarthritis (OA) served as controls.

Results—26 subjects met entry criteria and had a synovial biopsy (25 knee, 1 wrist). 16/26 (62%) were PCR-positive for either Ct or Cpn DNA, 10/16 (63%) for Ct, 4/16 (25%) for Cpn, 2/16 (13%) for both. These patients were significantly more likely to be PCR-positive compared to patients with OA (20/167 [12%]; $p < 0.0001$). No specific clinical characteristics differentiated PCR-positive from PCR-negative subjects. 4/26 (15%) subjects were PCR-positive in PBMC (3 Ct; 1 Cpn), 2 of which also were PCR-positive in synovial tissue (1 Ct; 1 Cpn). No significant correlation between PCR-positivity and HLA-B27-positivity was found.

Conclusion—The synovial tissue PCR-positivity rate in subjects with uSpA identified here is significantly higher than that found in the synovial tissue of subjects with OA. This result suggests that chlamydial infection, often occult, may be etiologic for uSpA in many patients.

In 1978, a group of rheumatoid factor-negative inflammatory arthritidies were recognized as a unified entity and termed Seronegative Polyarthrtitis (1). Now known as the spondyloarthropathies (SpA), these are a group of arthritidies that share clinical and radiographic features. The SpA's include ankylosing spondylitis (AS), psoriatic arthritis,

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inflammatory bowel disease-related arthritis, reactive arthritis (ReA), and undifferentiated SpA. The term undifferentiated spondyloarthritis (uSpA) is used to designate patients with clinical and radiographic features consistent with the SpA's, but who do not fulfill the classification criteria for any of the established disease categories.

In 1991, the European Spondyloarthropathy Study Group (ESSG) criteria were developed in order to establish diagnostic criteria for the SpA's (2). These criteria include both clinical and radiographic features and have been demonstrated to be 87% sensitive and specific for the diagnosis of SpA. They are somewhat less well suited for diagnosis of early disease but are extremely useful for established disease. In 1995, the Amor criteria were developed for SpA, which employ many of the same clinical and radiographic features as the ESSG criteria, but they also include HLA-B27 as part of the diagnostic panel (3).

The prevalence of SpA in Caucasian populations is estimated to be 0.5-2.0% (4). The true prevalence of uSpA is difficult to assess quantitatively in these or other groups because of a lack of specific diagnostic criteria and the fact that it is often unrecognized. However, AS and uSpA are considered to be the most common types of SpA (5,6). Indeed, a large study assessing the prevalence of SpA's in Germany demonstrated an overall prevalence of 1.9%, with AS being the most common type (0.86%) followed by uSpA (0.67%) (7). Another report indicated that uSpA was more than twice as common as AS, with 40% of the subjects having the former condition (8). Importantly for the study described here, uSpA may well be the most underdiagnosed type of SpA. For one example, a study in Spain in 2000 evaluated 514 patients with anterior uveitis and found that 53% of these patients were not diagnosed with a SpA until after their first episode of uveitis; the percentage was 91% in uSpA (9).

We and others have argued that the term uSpA should be viewed solely as a working label (10). The onus remains on us as clinicians and researchers to solve the clinical conundrum. This is often done by long-term follow up, which can take years during which the patient often develops disease sequelae before a definitive diagnosis is made. Conversely, identification of a causative organism, if present, allows an immediate diagnosis.

It has been argued that uSpA is a *forme fruste* of ReA (11). *Chlamydia trachomatis* (Ct) is the most common etiologic agent causing ReA in the U.S. (12,13), and the initial infection is often asymptomatic (14,15). A number of published studies also indicate that *Chlamydophila (Chlamydia) pneumonaie* (Cpn), a related respiratory pathogen, is another causative agent in ReA, albeit at a lower frequency (16,17). The aim of the present study was to determine the percentage of patients with uSpA whose disease may be a result of infection with Ct and/or Cpn. To address this question, we assessed the prevalence of synovial Ct and Cpn in patients who met the ESSG criteria for SpA without evidence of AS, psoriasis, inflammatory bowel disease, or preceding dysentery.

PATIENTS AND METHODS

Subjects and controls

Individuals were recruited from May 2006 through December 2007 as part of an ongoing clinical trial to assess a novel therapy for patients with chronic *Chlamydia*-induced ReA (ClinicalTrials.gov Identifier: NCT00351273). Clinical study sites were: University of South Florida College of Medicine (Tampa, FL), Louisiana State University Health Sciences Center (New Orleans, LA), and University of Toronto (Toronto, Canada). Subjects were enrolled in this trial if they had chronic uSpA or classic CiReA. All subjects had to meet the ESSG criteria of SpA (2) without evidence of AS, psoriasis, inflammatory bowel disease, or preceding dysentery. Subjects could be male or female, at least 18 yr of age, and symptoms had to be present for at least 6 months; subjects had to meet these inclusion criteria:

A. Inflammatory Spinal Pain (Definition: spinal pain in back, dorsal, or cervical region, with at least four of the following: (a) onset before the age of 45, (b) insidious onset, (c) improved by exercise, (d) associated with moming stiffness, (e) at least 3 mo duration) **Or**

B. Synovitis **and** one or more of the following (criteria C — G)

C. Positive family history (Definition: presence in first-degree or second-degree relatives of any of the following: (a) ankylosing spondylitis, (b) psoriasis, (c) acute uveitis, (d) reactive arthritis, (e) inflammatory bowel disease)

D. Urethritis or cervicitis within 1 month before arthritis

E. Alternating buttock pain

F. Enthesopathy (Definition: past or present spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia)

G. Sacroiliitis (Definition: at least grade 2 unilateral; radiographic grading system: 0 = normal, 1 = possible, 2 = minimal, 3 = moderate, 4 = ankylosis)

Exclusion criteria included use of anti-coagulates, current pregnancy, and previous prolonged exposure to antibiotics (> 2 wk) as a specific therapy for possible ReA.

Synovial tissue samples from APH's freezer library were used as controls for this study. These were procured from patients with osteoarthritis (OA) using the Parker-Pearson method (18) or at the time of joint replacement. No PBMC were available from OA. PCR results from synovial tissue samples are employed as the primary outcome measure. PBMC PCR results also are reported.

Sample Procurement and Handling

One 5 ml blood sample was obtained from each study subject and shipped from the clinical sites to the laboratory at ambient temperature *via* overnight courier. From subjects with active synovitis and who gave consent, synovial tissue was obtained at the same time by blind synovial biopsy using a Parker-Pearson needle (18). The site biopsied was the knee in all subjects with the exception of one sample obtained from the wrist by open surgical procedure. 3-4 tissue samples were obtained from in sterile fashion from the suprapatellar pouch from each subject (except the wrist). These samples were immediately snap-frozen in liquid nitrogen and stored at -80°C until shipping to the laboratory on dry ice, again using overnight courier.

Data Collection

On the day of synovial biopsy, data collected included standard demographics, a history and physical examination, the blood sample, HLA-B27 status, and any known previous exposure to Ct or Cpn. If the subject had such an exposure, the timing of that infection was documented in relation to the onset of their uSpA. The physical examination included swollen and tender joint counts (66 and 68 joints, respectively), evaluation for dactylitis and active enthesitis (Achilles tendonitis or Plantar fasciitis), and a skin examination (specifically for keratoderma blenorrhagicum and circinate balanitis).

PCR Analysis

PCR assays to assess chlamydial DNA in synovial or other samples have been published for both *C. trachomatis* and *C. pneumoniae* and were done as described for the present study (19-25). Screening PCR assays are done in duplicate by each of two workers, and standard analyses include assays targeting at least two different DNA sequences from each organism.

The Ct-directed assays target *omp1* and the 16S rRNA genes. Assays to assess the presence of Cpn DNA target the homologous genes in that organism; Ct-directed primer systems do not amplify sequences in Cpn, and *vice-versa*. Samples were considered positive if both duplicates in all assays agree. In the case of discrepancies, a third set of assays targeting any of several other genes is used for resolution. Extreme care was taken to avoid contamination of PCR-related materials.

Statistical Analysis

Subjects with uSpA whose synovial tissue was positive for *Chlamydia* were compared to subjects with OA using the Fisher's exact test. P-values of 0.05 or less were considered significant.

RESULTS

A total of 80 study subjects were screened as part of the therapeutic clinical trial for *Chlamydia*-induced ReA. Of these 80, 26 met the entry criteria and underwent a synovial biopsy. These synovial tissue samples were obtained at the University of South Florida College of Medicine and Louisiana State University Health Sciences Center. Demographic information for the study subjects is summarized in Table 1. The study subjects' (16M/10F) average age and disease duration were 48.4 years (range 22-70) and 9.1 years (range 0.5-36), respectively. In 25 of the study subjects, the knee was the site of synovial biopsy; the remaining subject's biopsy site was the wrist. All joints biopsied had active synovitis on the day of synovial tissue procurement. The control group for this study comprised 167 patients with OA (Table 1).

As indicated above, all study subjects met the ESSG criteria, and all had disease duration of 6 months or longer. Specific clinical characteristics on the day of the synovial biopsy are summarized briefly in Table 2. The average physician and patient global assessment for all 26 subjects was 57.7 (0 being the best and 100 the worst) and 41.6 (0 being the worst and 100 the best), respectively. 16/26 (62%) of the subjects had a dedicated radiograph of sacroiliac joints at the time of study entry. 14/16 (88%) of the subjects with sacroiliac radiographs had asymmetric sacroiliitis of Grade 2 or Grade 3. No subject had Grade 4 radiographic sacroiliitis or symmetric sacroiliitis. Seven subjects were on a disease modifying anti-rheumatic drug for their SpA at the time of biopsy (3 sulfasalazine, 2 methotrexate, and 2 hydroxychloroquine).

16/26 (62%) study subjects were PCR-positive for either Ct or Cpn DNA in multiple assays using synovial tissue nucleic acid preparations (Table 3). Of the positive biopsies, 10/16 (63%) were positive for Ct only, 4/16 (25%) were positive for Cpn only, and 2/16 (13%) were positive for both. These subjects were significantly more likely to be PCR positive for *Chlamydia* in their affected synovial tissue compared to synovial tissue from subjects with OA (20/167 [12%]; $p < 0.0001$). Interestingly, only 2/26 (8%) of the subjects had a possible Ct infection within 6 weeks of the onset of symptoms. Because we had no documented proof of the original Ct infection or evidence of the actual timing of the infection; these two subjects were not originally classified as CiReA. Seven of the remaining 10 subjects (70%) who were PCR positive for Ct in synovial tissue had no known history of infection with the organism at any time in their lives. No subject had a known history of Cpn. None of the specific clinical characteristics of these study subjects (Table 2) or their medications significantly correlated with synovial tissue PCR- positivity, including a history of Ct at any time ($p=0.25$). Both subjects who had a history of Ct within the 6 weeks prior to the onset of uSpA were PCR-positive for Ct in synovial tissue, but the numbers were too low to determine if this was a significant correlation.

As stated, each synovial tissue sample was PCR-analyzed for the presence of two genes (specifically *omp1* and 16S rRNA in the case of Ct) in duplicate by two observers. This resulted in 8 assays per synovial tissue sample. Only those samples that were PCR-positive in all assays (8/8-positive) were considered a true positive. There were no uSpA or OA subjects who had some positive PCR assays (i.e. between 1/8 and 7/8 PCR-positive assays). Although 3-4 synovial tissue samples were obtained from each subject, we did not individually assay more than a single tissue sample in order to conserve these samples for future studies.

The disease duration was known for only 70/167 OA subjects (Table 3). Many of these subjects had their synovial tissue obtained at the time of arthroscopy for routine clinical care. OA disease inception was defined as the time of initial diagnosis by a physician. These factors contributed to the short disease duration and relatively young age of the OA subjects.

Only 4/26 (15%) subjects were PCR positive for chlamydiae in PBMC (3 Ct; 1 Cpn). Of those, 2 were PCR-positive in synovial tissue (1 Ct; 1 Cpn); both of these subjects' PBMC PCR was positive for Ct. 4/25 (16%) subjects were HLA-B27-positive (test not performed on one subject); all 4 were PCR-positive in synovial tissue (3 Ct; 1 Cpn), but there was not a significant correlation [p=0.26].

DISCUSSION

uSpA is one of the most common forms of SpA, and some data suggest that it is the *most* common presentation of all the SpA's (8). Chlamydial infections are the most common cause of ReA (12,13), although the initial infection frequently can be asymptomatic (14,15). Importantly for the present study, uSpA has been argued to be a *forme fruste* of ReA (11). The data presented here demonstrate that the rate of PCR-positivity in synovial tissue from patients with uSpA (62%) is significantly higher than that found in synovial tissue from subjects with OA (12%), suggesting that chlamydial infection, often occult, may be etiologic for uSpA in many patients. We note that background PCR-positivity rates of about 5-20% for Ct in synovial samples have been reported (26,27), and that subjects with suspected CiReA have higher rates of urogenital cultures for Ct compared to other types of SpA's (28).

New genital infections with Ct must be reported to the CDC, and that institution has estimated that as many as 3 million such new cases/year occur in the US, with as many as 4-6 million cases active at any one time (29,30). Reports have indicated that about 5% of patients develop objective features consistent with ReA after a Ct or nongonococcal infection (e.g., 31). If 5% of the 3 million individuals develop ReA, as many as 150,000 cases of acute *Chlamydia*-induced ReA would obtain in the US each year; this estimate is low, since it does not include cases that result from Cpn. About 30-50% of the 150,000 individuals would progress to chronicity; one study suggested 63% of patients experience chronic symptoms (32). For comparison, the estimated annual incidence of rheumatoid arthritis (RA) in the US is 44.6/100,000 (33). If the population is about 281 million (2000 US census figure), about 125,000 new cases of RA/year occur. A 2002 study in Sweden found the annual incidence of ReA to be higher than that of RA (34). Thus, *Chlamydia*-induced ReA represents a considerable burden on the US health care system and that of other nations, and its impact on those systems well may be significantly under-recognized.

The pathologic sequelae of chlamydial infections can be severe, and this is an issue of importance especially in women, where initial genital infections with Ct are often asymptomatic. Interestingly, 78% of subjects in one study who developed ReA features after Ct or nongonococcal infections had an asymptomatic initial infection (31). This mirrors the data reported here that 14/16 (88%) of subjects with a PCR-positive synovial tissue assay for

Ct had an asymptomatic initial infection. For Cpn, as many as 70% of acute infections are asymptomatic (35,36); even when the patient is symptomatic from an acute Cpn exposure, definitive identification of the organism is rare. Thus, relying on identification of a symptomatic infection will result in routine under-diagnosis, or misdiagnosis, of *Chlamydia*-induced ReA.

Because ReA is a type of SpA and the majority of patients with ReA do not present with the classic triad of symptoms (13), the contention that Ct could function etiologically to engender uSpA is reasonable. Although there is no pathognomonic diagnostic test for *Chlamydia*-induced ReA, documenting chlamydial DNA presence by PCR in synovial tissue of patients who fulfill the clinical criteria for ReA represents the most accurate means of diagnosing the condition. The contention that synovial tissue analysis yields the most accurate results is supported by the fact that the majority (85%) of the subjects studied here were PCR-negative in PBMC samples, and only 12.5% (2/16) patients PCR-positive for Ct in synovial tissue were PCR-positive in their PBMC.

Although there were significantly fewer OA subjects PCR-positive for chlamydiae, a small percentage (12%) did harbor this organism in their synovial tissue. As stated, similar findings have been reported in other OA subjects (27) and even a very small percentage of asymptomatic volunteers (26). This highlights the importance of host genetic variability and host tolerance. Various hosts might respond differently to the same pathogen. Further, in the case of Ct, there are several different serovars; these different serovars may portend diverse prognoses that include variable pathogenic sequelae. The study herein does not address these important questions. The fact that a small percentage of OA subjects' synovial tissue was PCR-positive for chlamydiae does not decrease the importance that significantly more uSpA subjects' synovial tissue were PCR-positive.

We note that only 16% (4/25) of the subjects studied, and only 25% (4/16) of those subjects with a PCR-positive synovial biopsy, were HLA-B27 positive. These numbers are lower than that indicated as HLA-B27 background prevalence in patients with ReA. However, the majority of epidemiological studies in ReA suggest that background prevalence is 30-50%, rather than the higher prevalences frequently reported (e.g., 13). Further, HLA-B27-negative patients who develop *Chlamydia*-induced ReA may display a less fulminate disease course or be less likely to manifest the complete triad of symptoms. The fact that the majority of these subjects were HLA-B27-negative might explain the less "classic" symptoms of ReA present, thereby adding to the clinical conundrum. Regardless, the data presented here suggest that chlamydial infections, often occult, are etiologic for many patients with uSpA.

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Table 1

	uSpA Subjects (n=26)	Osteoarthritis Controls (n=167)
Mean Age (range)	48.4 years (22-70)	43.3 (21-74)
Gender	16 males; 10 females	95 males, 72 females
Race	19 Caucasian 6 African American 1 Hispanic	125 Caucasian 25 African American 7 Hispanic 5 Asian 5 unknown
Mean Disease Duration (range)	9.1 years (0.5-36 yr)	1.1 years (0.1-2 yr) N=70
HLA-B27 Positive	4 (16%)	TNP

N/A: not applicable

TNP: test not performed

Table 2

	uSpA Study Subjects (n=26)
Axial Arthritis*	19 (73%)
Peripheral Arthritis	26 (100%)
Mean Swollen Joint Count (range)	3.3 (1-8)
Mean Tender Joint Count (range)	7.2 (1-26)
Active Enthesitis**	15 (58%)
Active Dactylitis	7 (27%)
History of Uveitis	2 (8%)
Active Uveitis	1 (4%)
History of Keratoderma Blenorrhagicum	6 (23%)
Active Keratoderma Blenorrhagicum	4 (15%)
History of Circinate Balanitis [16 males]	2 (13%)
Active Circinate Balanitis [16 males]	1 (6%)
Active Urethritis	1 (4%)
Mean Health Assessment Questionnaire (range)	0.89 (0-1.63)
Low Back Morning Stiffness	1.1 hours (0-2.5)
History of Ct at any time	11 (42%)
History of Ct within 6 weeks of uSpA onset	2 (8%)
Known history of Cpn	0 (0%)

* Axial Arthritis defined as per criterion “A” in the ESSG Criteria.

** Enthesitis = Achilles tendonitis and/or plantar fasciitis.

Table 3

	uSpA Study Subjects (n=26)	Osteoarthritis (n=167)	P-value
Synovial tissue positive for *Chlamydia* (Ct or Cpn or both)	16 (62%)	20 (12%)	<0.0001
Synovial tissue positive for *Chlamydia trachomatis* (Ct) only	10 (38%)	19 (11%)	0.001
Synovial tissue positive for *Chlamydophila pneumoniae* (Cpn) only	4 (15%)	0 (0%)	0.0003
Synovial tissue positive for both Ct and Cpn*	2 (8%)	1 (0.6%)	0.048

* Note: these subjects are included in the two rows above