Attack Rate of *Chlamydia*-induced Reactive Arthritis and Effect of the CCR5-Delta-32 Mutation: A Prospective Analysis

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ABSTRACT. ***Objective.*** Factors that predispose patients to *Chlamydia*-induced reactive arthritis (CiReA) are poorly defined. Data indirectly suggest chemokine receptor-5 (CCR5)-delta-32 mutation might play a role in CiReA. We investigated the attack rate of CiReA and we hypothesized that the CCR5-delta-32 allele may modulate disease susceptibility.

Methods. Patients who tested positive for *Chlamydia trachomatis* after either (1) symptoms of an acute venereal disease or (2) sexual contact with an individual known to be positive for the same organism were followed in a prospective fashion. All patients were contacted at Week 6 after their acute infection and queried for symptoms of CiReA. Patients who had new-onset symptoms suggestive of CiReA were followed at Weeks 12, 26, and 52. All subjects were tested for CCR5-delta-32 mutation.

Results. A total of 365 study participants were enrolled, with average age 24.4 years, 201 men (55%) and 164 women (45%). We followed up with 149 patients (41%) at Week 6. Twelve of 149 participants (8.1%) had symptoms suggestive of CiReA at Week 6. None of these 12 patients was positive for the CCR5-delta-32 mutation. Of the 12 patients that had symptoms at Week 6, we were able to follow up with 7 through Week 52. All 7 had complete resolution of their symptoms by Week 26. Overall, 25/365 (6.8%) subjects were positive for the CCR5-delta-32 mutation.

Conclusion. The attack rate of CiReA in our study was higher than previously reported, but the CCR5-delta-32 mutation does not seem to play a role in CiReA disease susceptibility. (First Release July 1 2013; J Rheumatol 2013;40:1578–82; doi:10.3899/jrheum.130136)

Key Indexing Terms:
REACTIVE ARTHRITIS *CHLAMYDIA* CCR5-DELTA-32 MUTATION

Reactive arthritis (ReA) is an inflammatory arthritis that arises after certain genitourinary or gastrointestinal infections. Bacteria that are known to cause ReA include *Chlamydia trachomatis* (Ct), *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*. ReA develops within 2–6 weeks after a triggering infection. However, only a minority of patients develop ReA after they are exposed to these organisms. The attack rate of ReA ranges from 1.5%[1] to about 30%[2]; however, all these studies except 1 analyzed patients with postdysentery ReA. These data also demonstrate that certain enteric organisms appear to be more likely to cause ReA than others[3], suggesting various arthritogenic potential of the different enteric organisms. The only study that has assessed the attack rate of *Chlamydia*-induced ReA (CiReA), specifically, demonstrated an attack rate of 4.1%[4]. Because Ct is the most common trigger of ReA[3], and emerging data demonstrate that asymptomatic Ct infections can also cause CiReA[5], it is necessary to better define the attack rate of CiReA.

It is well established that a large percentage of patients who develop ReA will experience spontaneous resolution of symptoms within 6 months, reportedly 50%–90% of the time[3]. Because only a minority of patients exposed to Ct will develop CiReA and the majority of these patients will experience spontaneous remission, the question arises, what predisposes to disease susceptibility and chronicity?

It is known that HLA-B27 is important in the pathogenesis in the spondyloarthropathies (SpA). While HLA-B27 does seem to play a part in the development of ReA, it is certainly not the sole determinant. HLA-B27 prevalence in patients with ReA ranges from 30% to 50%[3]; some studies show no increased prevalence of this antigen in patients with post-*Campylobacter*-induced ReA[6]. Clearly there are factors other than HLA-B27 that influence the

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susceptibility of developing ReA and the disease course it follows.

Chemokines are critical for the inflammatory process in autoimmune diseases such as ReA. The chemokine receptor-5 (CCR5) mediates chemotaxis and is expressed by lymphocytes with the Th1 phenotype and monocyte/macrophages. The CCR5 protein is a cell-surface receptor that binds several chemokines. A 32 base-pair deletion in the CCR5 (CCR5-delta-32 allele) abolishes receptor expression in homozygotes, while CCR5-delta-32 carriers would express less functional receptor than wild-type homozygotes. This polymorphism is related to the resistance to human immunodeficiency virus (HIV)-1 infection and progression toward acquired immunodeficiency syndrome[7,8,9]. Some data also suggest a role for CCR5-delta-32 mutation in the pathogenesis of *Yersinia pestis* infection[10], although this remains controversial. Data suggest that the CCR5-delta-32 mutation might be important in determining disease severity in other autoimmune conditions such as rheumatoid arthritis (RA) and sarcoidosis[11,12,13]. Further, evidence from mice and humans suggests that inflammation associated with CCR5 function may predispose to development of tubal infertility after a *Chlamydia* infection[14], and we recently demonstrated that this mutation increases the synovial burden of *C. trachomatis* in infected individuals[15]. Lastly, data indicate that ReA is more prevalent in whites and the CCR5-delta-32 mutation is much more prevalent in those of European descent[16]. We hypothesized that the CCR5-delta-32 allele may modulate susceptibility and disease chronicity in CiReA.

To better define the attack rate of CiReA, including patients with asymptomatic Ct infections, and to assess the role that the CCR5-delta-32 allele might play in CiReA susceptibility and chronicity we recruited patients from a communicable disease clinic with both symptomatic and asymptomatic Ct infections. We followed them with telephone surveys assessing for signs or symptoms consistent with CiReA. All subjects were tested for the CCR5-delta-32 allele. Because this was an unfunded study, we were limited in the amount of testing/analyses we could perform on these study participants.

MATERIALS AND METHODS

Patients. Eligible patients were men and women 18–75 years of age who tested positive for *C. trachomatis* after either symptoms of an acute venereal disease or sexual contact with an individual known to be positive for the same organism. *C. trachomatis* testing was performed by either gram stain or direct cell culture of endocervical swabs from women or urethral swabs from men, or DNA probe using nucleic acid amplification tests of endocervical swabs from women, urethral swabs from men, or urine from men or women. Patients were excluded if they were unable or unwilling to provide informed consent or if they had a history of RA, systemic lupus erythematosus, or another type of inflammatory arthritis. Patients were recruited from the Hillsborough County Department of Health, Tampa, Florida, which is affiliated with the University of South Florida College of Medicine.

Study design. All participants were followed in a prospective fashion. With informed consent, 2 blood samples were collected. Samples were stored frozen at –70°C to be tested for the CCR-5-delta-32 mutation at a later time. Subjects were queried as to the details of their Ct infection at that point. The data obtained included patient demographics [age, sex, race, medical history including history of sexually transmitted diseases (STD)], length of symptoms of their current infection (if present), and any treatment for their current symptoms (if present). Our study was approved by the governing institutional review board at the University of South Florida College of Medicine.

We attempted to contact all these participants 6 weeks after their acute Ct infection to perform a telephone survey. All telephone surveys were conducted by rheumatology subspecialty residents (AR and JPG). Those contacted at Week 6 were queried by telephone for any new arthritis symptoms or other symptoms of CiReA such as conjunctivitis, uveitis, enthesitis, etc. A standard questionnaire of 13 questions was administered to each of these participants at Week 6. They were queried about any new peripheral or axial arthritis since their Ct infection. Of those that gave a positive response, the participants described their new-onset arthritis in more detail using a standardized approach as outlined in this questionnaire. This included specific joint(s) involved and the associated symptoms. Subjects were also queried about any new eye/vision problems, new-onset heel pain, persistent dysuria, or new rash involving the palms and/or soles. Specific details were obtained for any positive responses. This telephone questionnaire included all the European Spondylarthropathy Study Group (ESSG) criteria with the exception of plain radiographs of the sacroiliac joints. If the participant described no new symptoms consistent with CiReA at their Week 6 interview, their participation in the study was complete at that point.

Any subject who described new-onset arthritis or other symptoms consistent with CiReA at their 6-week telephone interview had followup telephone interviews at Weeks 12, 26, and 52 to follow the chronicity of their symptoms. A questionnaire similar to the one used with the Week 6 survey was used for these interviews. All study subjects with symptoms consistent with CiReA were followed for a total of 52 weeks. Figure 1 illustrates the study design.

As per the original protocol, we attempted to bring in all participants with possible or probable CiReA (per their 6-week telephone interview) for evaluation with a rheumatologist in order to confirm the findings and establish a definitive diagnosis of CiReA. However, we were able to persuade only 1 of the first 6 subjects with possible/probable CiReA to come in for an examination and history, so the protocol was amended to rely on the telephone interviews. Because of this limitation, we described all subjects with a positive 6-week telephone questionnaire as having possible/probable CiReA, but the ESSG criteria were applied to all participants with symptoms suggestive of CiReA at Week 6.

Testing. Blood was obtained by venipuncture and stored at –70°C in standard fashion from all study participants. Frozen blood samples were shipped overnight on dry ice to the laboratory for DNA preparation and subsequent analysis of the CCR5-delta-32 mutation using a standard PCR-based method[15]. The results of the CCR5-delta-32 mutation assay were kept blinded from those performing the telephone surveys of study participants until the study was completed.

Statistical analysis. Our study was designed as a prospective analysis comparing the prevalence of the CCR5-delta-32 mutation in individuals who develop CiReA after an acute Ct infection to those who do not develop CiReA after acute Ct infection. It was our hypothesis that this mutation would be significantly increased in those with CiReA. The prevalence of the CCR5-delta-32 mutation is known to range from about 5% to 15%[16]; however, these data are from studies of people of European descent. This same mutation is much less common in other populations, specifically Africans[16]. Given the patient population we studied, we anticipated that the background prevalence would be on the low side of the stated range (i.e., 5%). We assumed that 50% of the subjects who developed CiReA would

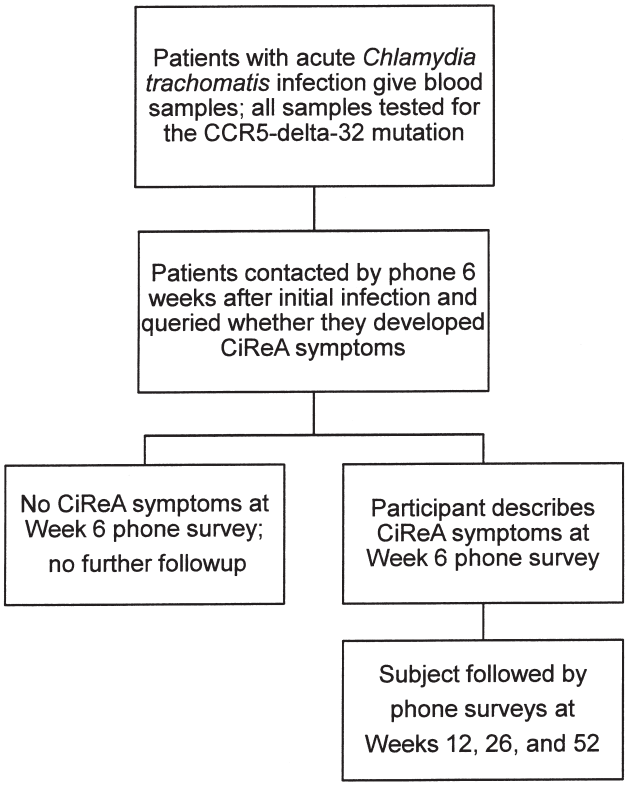

Figure 1. The study design. All subjects with symptoms consistent with *Chlamydia*-induced reactive arthritis (CiReA) were followed for a total of 52 weeks. CCR5: chemokine receptor-5.

test positive for this mutation. Using Fisher's exact test, we set out to recruit at least 8 subjects who would develop CiReA by Week 6 to be compared to the control population to demonstrate a statistically significant effect of the mutation and CiReA susceptibility. To recruit 8 subjects with CiReA, we needed to contact at least 160 subjects (attack rate of 5%) with the Week 6 telephone survey. We anticipated being able to contact 50% of the study participants with the Week 6 telephone survey, leading to a sample size of 320 participants.

As the study progressed, we discovered we were contacting about 41% of the subjects at their Week 6 telephone survey so we increased our sample size to 365 enrolled subjects in an attempt to meet our goal of 160 subjects contacted at Week 6.

RESULTS

Study subjects were enrolled from July 2006 through April 2009. In total, 365 subjects were enrolled, with a mean age of 24.4 years. There were 201 (55%) men and 164 (45%) women; 231 (63%) were African American, 81 (22%) Hispanic, 48 (13%) white, and 5 (1.3%) others. We found that 242/365 (66%) of enrolled subjects had an asymptomatic *C. trachomatis* infection; 150/365 (41%) were referred for testing because of recent sexual contact with an individual known to be positive for the same organism. Sixty-two of 365 participants (17%) had a previous STD; of these, *C. trachomatis* was the most common (n = 39), followed by *N. gonorrhea* (n = 20). Two subjects were known to be positive for HIV. All subjects were treated for their acute *C. trachomatis* infection with antibiotics as per their standard of care.

Followup. We were able to contact 149 (41%) study subjects at Week 6; 12/149 (8.1%) of them had symptoms consistent with CiReA (Table 1). None of these 12 patients had the CCR5-delta-32 mutation. Ten of these 12 participants met the ESSG diagnostic criteria for spondyloarthritis (Subjects 6 and 12 did not). Seven of these 12 subjects were female and 8 had initial asymptomatic *C. trachomatis* infections. Two of these subjects had a previous STD and both were *C. trachomatis* infections (Subjects 7 and 9). None of these 12 subjects was known to be HIV-positive.

Regarding the chronicity of these 12 subjects' symptoms, we were able to followup with 7 at Weeks 12, 26, and 52. All 7 had complete resolution of their symptoms by Week 26 and remained asymptomatic at Week 52.

Prevalence of CCR5-delta-32 mutation. Overall, 25/365 (6.8%) subjects were positive for the CCR5-delta-32 mutation. All subjects who tested positive were heterozygous for the mutation. The average age of these 25 subjects was 24.2 years and 14 were males. Regarding the prevalence of the CCR5-delta-32 mutation by ethnicity in the overall patient population, 9/231 (3.9%) African Americans, 4/81 (4.9%) Hispanics, and 12/48 (25%) whites were heterozygotes. We were able to followup with 11 (44%) of these 25 patients with a Week 6 telephone survey. None had symptoms suggestive of CiReA at the Week 6 followup.

DISCUSSION

In this study, we enrolled 365 patients with acute *C. trachomatis* infections and contacted them 6 weeks later to see how many developed signs or symptoms consistent with CiReA. We were able to followup with 149 of these subjects and 12 (8.1%) developed possible or probable CiReA (10/12 met the ESSG criteria). However, none of these 12 subjects had the CCR5-delta-32 mutation so it does not appear that this mutation plays a role in the disease susceptibility of CiReA. Because this mutation is more prevalent in whites, and only 1/12 subjects with possible/probable CiReA was white, it is difficult to truly determine the effect of this mutation on the incidence of CiReA in this specific population. In addition, because no subject with longterm followup developed chronic disease, the potential role this mutation might play in disease chronicity remains uncertain.

Although this was a negative study, it produced several significant findings. We are aware of only 1 other study that followed patients after a *C. trachomatis* infection to observe how many would develop CiReA[4]. That study queried 217 subjects with possible or proven *C. trachomatis* infection by mail 6 weeks after their infection, and found that 4.1% of patients developed ReA. Importantly, our study followed the subjects in a prospective fashion and included only those with a definite *C. trachomatis* infection. We documented a

Table 1. Disease characteristics of subjects with *Chlamydia*-induced reactive arthritis (CiReA).

Pt	Sex	Race	Age, yrs	Mode of Ct Diagnosis	Initial Ct Symptoms	Week 6 Symptoms	Week 12 Symptoms	Week 26 Symptoms	Week 52 Symptoms
1	F	AA	18	DNA probe	Discharge × 3 wks	Left shoulder arthritis; plantar fasciitis	Lost to FU	Lost to FU	Lost to FU
2*	M	H	27	Gram stain and culture	None	Conjunctivitis; circinate balanitis; right knee arthritis; left lateral epicondylitis	Circinate balanitis	Resolved	Resolved
3	F	AA	22	Gram stain and culture	None	Bilateral hand arthritis	Resolved	Resolved	Resolved
4	F	AA	18	DNA probe	Pelvic pain	Low back pain; left knee arthritis; left Achilles tendonitis	Low back pain; left knee arthritis	Resolved	Resolved
5	F	AA	18	Gram stain and culture	None	Bilateral ankle arthritis	Bilateral ankle arthritis (improved)	Resolved	Resolved
6	F	AA	20	Gram stain and culture	None	Bilateral knee arthritis	Bilateral knee arthritis	Resolved	Resolved
7	F	AA	21	DNA probe	None	Left hip arthritis	Left hip arthritis	Lost to FU	Lost to FU
8	M	AA	67	DNA probe	Penile discharge × 1 wk	Bilateral knee, ankle, feet arthritis; bilateral Achilles tendonitis; keratoderma blennorrhagicum	Lost to FU	Lost to FU	Lost to FU
9	F	AA	30	DNA probe	None	Low back/buttock pain/ stiffness; medial epicondylitis	Low back/buttock pain/stiffness	Resolved	Resolved
10	M	H	26	Positive *C. trachomatis* contact	None	Low back/buttock pain/ stiffness; bilateral knee pain; left plantar fasciitis	Bilateral knee pain; left plantar fasciitis	Right knee pain (mild)	Resolved
11	M	White	24	Positive *C. trachomatis* contact	Penile discharge × 4 days	Left knee arthritis; right ankle arthritis and Achilles tendonitis; conjunctivitis	Lost to FU	Lost to FU	Lost to FU
12	M	AA	29	Positive *C. trachomatis* contact	None	Left hip arthritis; left knee arthritis	Lost to FU	Lost to FU	Lost to FU

* Patient 2 was examined by a rheumatologist at Week 6 confirming the clinical symptoms. Patients 3 and 7 had a first-degree family relative (Patient 5) who had psoriasis and Crohn disease. Ct: *Chlamydia trachomatis*; AA: African American; H: Hispanic; FU: followup.

higher attack rate of 8.1%. The previous study and ours were in agreement that the majority of patients who developed CiReA did so after an initial asymptomatic infection. Considering there is no diagnostic test for CiReA, or ReA in general, and the literature is replete with evidence that healthcare practitioners place too much emphasis on the "classic triad" of symptoms and/or the presence of the HLA-B27 antigen to make the diagnosis[3], the fact that asymptomatic initial infections might be a more common trigger only clouds this diagnosis further.

It is also generally believed that post-chlamydial ReA is far more common in men[17]. However, 7/12 subjects in our study who developed possible/probable CiReA were female, while the majority of the population studied was male. The literature also suggests that CiReA is more common in whites[18] and the HLA-B27 antigen is more prevalent in this same population. While it is important to keep in mind that 63% of the overall patient population was African American, 9/12 (75%) of the patients who developed CiReA, including all 7 female subjects, were African American. Only 1/12 subjects with CiReA was white. Although this study was not powered to compare the incidence or attack rate of CiReA in these different groups, these data do challenge some of the traditional paradigms of this condition.

While the prevalence of the CCR5-delta-32 mutation is well documented in European, Chinese, and African populations[16], the background prevalence of the mutation in North America is poorly described. To our knowledge, prevalence of this mutation has been analyzed in only 2 smaller studies in North America, one in patients with endstage renal disease in Canada[19] and one in a pediatric population with HIV in the US[20]. Our study demonstrates a consistent background prevalence of this mutation in North American

whites compared with Europeans and is the first to define the prevalence in a large population of African Americans.

Although this is the largest prospective study analyzing patients with CiReA after a documented acute *C. trachomatis* infection, there are limitations. We initially expected to contact at least 50% of the participants with their Week 6 telephone survey, but our contact rate was slightly lower. Considering the rapidly changing landscape of telecommunications (frequently changing cellphone numbers, etc.), this is not unexpected. Also, our study has a limitation similar to that of the previous study analyzing the attack rate of CiReA[4], in that the majority of the patient population was African American; therefore this might not be a true indication of the attack rate of CiReA after *C. trachomatis* infections. Indeed, the true attack rate might be higher if more whites were studied and the possibility remains that this same mutation might have an effect in this specific population. Future studies should attempt to power the analysis so these questions regarding the influence of race and sex on attack rate can be fully defined. Also, it would have been preferred to formally examine the patients with possible/probable CiReA, but as described above, we were unsuccessful at bringing these patients in for evaluation (with the exception of Subject 2). However, 10/12 of these subjects with suspected CiReA did meet the ESSG diagnostic criteria for spondyloarthritis; the 2 subjects that did not fulfill these criteria were judged to have CiReA based on expert opinion. Ideally, it might have proved useful to perform other testing on these patients, such as HLA-B27 or synovial tissue PCR analysis for *C. trachomatis*; however, more in-depth analyses or other laboratory testing were not possible.

Although CiReA represents the classic interplay between host and environment, it appears that the CCR5-delta-32 mutation does not provide any clues as to the underlying pathophysiology of this interaction. However, these data add significantly to existing literature regarding the attack rate of CiReA. CiReA appears be more common than we currently appreciate. Our study also questions some of the traditional paradigms regarding the incidence of CiReA in women and various racial backgrounds. Indeed, it is possible that CiReA represents a larger disease burden worldwide than is commonly acknowledged.

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