British Journal of Medicine & Medical Research
8(4): 353-361, 2015, Article no.BJMMR.2015.459
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

The Relation between Chronic Aseptic Arthritis and Previous Chlamydia Infection among Middle Aged Iraqi Patients

Asa'ad F. Albayati[1*], Sinan B. Alrifai[2], Wisal R. Al-Hayali[2] and Dhoha R. Al Taha[3]

[1]Department of Medical Microbiology, Al-Iraqia University, College of Medicine, Baghdad, Iraq.
[2]Department of Medical Microbiology, Tikrit University, College of Medicine, Salahaddin, Iraq.
[3]Salahaddin Health Directorate/Digla Hospital for Medical Rehabilitation, Salahaddin, Iraq.

Authors' contributions

This work was carried out in collaboration between all authors. Authors AFA and SBA designed the study, wrote the protocol, performed the spectroscopy analysis, managed data collection, and wrote the first draft of the manuscript. Authors WRAH and DRAT performed critical reviews on the manuscript, managed the experimental process, performed blood sample collection, and managed the statistical analyses of the study. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/17615
Editor(s):
(1) Roberto Manfredi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.
Reviewers:
(1) Anonymous, Japan.
(2) José Augusto Adler Pereira, Microbiology, Immunology and Parasitology Faculty of Medicine. State University of Rio de Janeiro, Brazil.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1116&id=12&aid=9077

Clinical Practice Article

Received 20th March 2015
Accepted 21st April 2015
Published 2nd May 2015

ABSTRACT

Aims: This study was conducted to detect and evaluate the relation between chronic aseptic arthritis and previous *Chlamydia trachomatis* infection among middle aged Iraqi patients.
Study Design: Cross sectional study
Place and Duration of Study: private clinic in Al-Door city/ Salahaddin Province / Iraq, between October 2012 and May 2013.
Methodology: This study included 33 known patients with chronic arthritis, with negative rheumatoid factor (RF) in their sera, aging from 26 to 61 years. Septic arthritis was excluded by history, clinical examination, and blood investigations. The ESR for these patients was estimated. Other 33 subjects were taken as a control group. *Chlamydia trachomatis* IgM and IgG were estimated by ELISA test (sandwich method) for both groups' sera, and results were statistically

**Corresponding author: Email: molarfast@gmail.com;*

analyzed.
Results: The female: male ratio in current study is (5.6: 1), with mean age of (46) years old. More than half of cases (52%) were having ESR value of 40-60. A highly significant statistical difference (P<0.001) was noticed between study groups in regard to *C. trachomatis* IgG mean levels in their sera calculated by unpaired T- test.
Conclusion: There is a significant relation between chronic arthritis and previous Chlamydia infection in current study (demonstrated by high titer of anti- *Chlamydia trachomatis* IgG).

Keywords: Chronic arthritis; Chlamydia trachomatis; IgM; IgG.

1. INTRODUCTION

Aseptic arthritis is precipitated by an extra-articular infection. The disease has attracted a great deal of research interest because it is a paradigm for a chronic rheumatic disease in which host immunogenetic susceptibility factors interact with a microbial trigger [1].

The dominant host factor is the class I HLA gene B27, which is present in 60-90% of such cases. The infections that initiate the disease are either Salmonella, Shigella, Campylobacter, and Yersinia spp., or infections with *Chlamydia trachomatis*. There have been numerous mechanisms postulated to explain this kind of arthritis, including molecular mimicry, immune response to arthritogenetic peptide, immune complex formation, *in situ* antigen deposition, and toxin-mediated synovitis [2].

All Chlamydia species are obligate intracellular bacterial parasites, and all are pathogenic to their various hosts [3]. A number of studies have also indicated that *Chlamydophila* (Chlamydia) *pneumoniae* is another, although less frequent, causative agent in arthritis [4,5].

Both species disseminate from their sites of primary infection, and when they do so, these organisms often take up long-term residence at distant anatomic locations. At sites of their dissemination, neither *C. trachomatis* nor *C. pneumoniae* produces any known toxins. Rather, both species may elicit a powerful immunopathogenic response that in turn can engender various diseases, one of which is inflammatory arthritis. Persistent chlamydial organisms exist in a morphologically aberrant, but metabolically active, state in synovial tissue [6,7].

Incidence of the disease is 5/100,000 patients aged 18-60 years [8]. A relatively small proportion of individuals who acquire a genital infection with *C. trachomatis* develop acute inflammatory (reactive) arthritis, and only a portion of those patients proceed to chronic disease [9].

Data on the use of PCR for the detection of intra-articular *C. trachomatis* varies between 0% and 100% positivity in patients with arthritis and undifferentiated spondyloarthropathy (uSpA) [10-13].

Furthermore, serological tests can be helpful in establishing past or present chlamydial infections. Also, in chronically infected patients in whom the bacteria are no longer detectable locally in the synovium, a positive serological test may be the only indication of chlamydial involvement [14].

2. MATERIALS AND METHODS

This study was conducted on 33 known patients with chronic arthritis for > 6 months, with negative rheumatoid factor (RF) in their sera, aging from 26 to 61 years. Other 33 subjects, aging from 22 to 60 years with nearly similar proportion between genders, have enrolled in this study as a control group, selected blindly to their medical conditions (apart from chronic arthritis and similar conditions). Table 1 shows the distribution of cases according to age. More than half of the study group cases (about 57%) were in age between 30 years and 49 years old, with mean age of (46) years old. The mean age of the control group is (45) years old.

Among the 33 cases, 28 were females, and the other 5 were males (female: male ratio is 5.6:1). Fig. 1 illustrates the distribution of cases according to gender.

Base line data about subjects were obtained from their history and clinical examination, a previously arranged questionnaire was used for this purpose. Table 2 shows the main clinical manifestations of the chronic arthritis group in current study.

Table 1. Age and gender distribution among current study cases

Age groups	Study group		Total	Control group		Total
	Male	Female		Male	Female	
20-29 years	1 (20%)	1 (4%)	2 (6%)	1 (16.7%)	1 (3.7%)	2 (6%)
30-39 years	-	8 (28%)	8 (24%)	1 (16.7%)	9 (33.3%)	10 (30%)
40-49 years	1 (20%)	10 (36%)	11 (33%)	1 (16.7%)	9 (33.3%)	10 (30%)
50-59 years	-	7 (25%)	7 (22%)	1 (16.7%)	6 (22.2%)	7 (22%)
≥60 years	3 (60%)	2 (7%)	5 (15%)	2 (33.2%)	2 (7.5%)	4 (12%)
Total	5(100%)	28(100%)	33 (100%)	6 (100%)	27 (100%)	33 (100%)

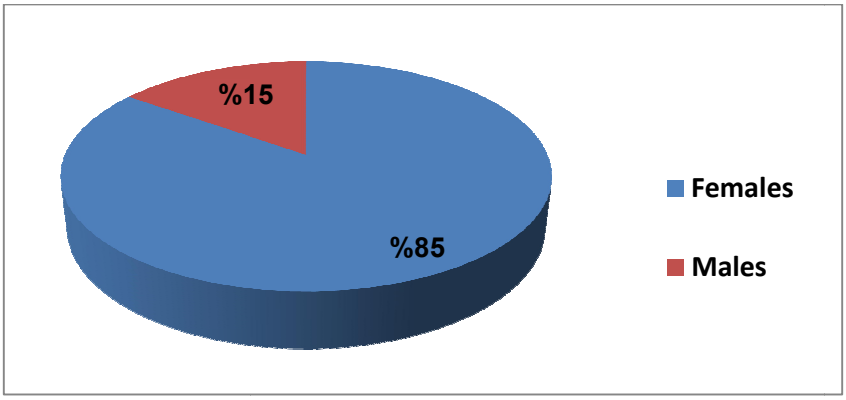


Fig. 1. The distribution of study group cases according to gender

Table 2. The criteria of inclusion and the clinical manifestations followed for selecting chronic arthritis cases in current study group [15]

Criteria followed for selecting chronic arthritis cases	General symptoms & signs of chronic arthritis
1. Arthritis (Asymmetric mono, oligo or polyarthritis, often affecting the lower extremities, that is not resolved for at least 6 months) 2. Enthethopathy (inflammation of the site of insertion of ligaments, tendons, joint capsule or fascia to bone, that is not resolved for at least 6 months).	Pain, Tenderness, Swelling, Morning stiffness, Limitation in movement, Deformity, and Fever.

Venous blood samples of about 5 ml were aspirated and collected in dry plain tubes. After taking part of blood to perform complete blood picture (CBP), erythrocyte sedimentation rate (ESR) and RF, blood in plain tubes allowed to clot (for minimum 30 minutes) at room temperature (20-25°C), then separated by centrifugation (3000 rpm for 5 minutes) to separate the serum and dispensed into sterile tightly closed Eppendrof tubes and stored at -20°C until assayed.

All sera samples were tested for CBP, RF, and ESR. Septic arthritis was excluded from all cases by history, clinical examination, and laboratory investigations (CBP; with no signs of bacterial infection). Also, RA was excluded by history, clinical examination, along with the negative RF in all samples sera.

The ESR values are illustrated in Fig. 2, where all cases show high ESR level (ESR ≥ 40). More than half of cases (52%) were having ESR value of less than 60.

Rheumatoid factor (RF) was tested using commercial Latex agglutination test method (Cortez Diagnostics Inc., California-USA) for qualitative and semi-quantitative measurement (based on reaction between human IgG bound to biologically inert latex particles and rheumatoid factors in the test serum specimen).

Both IgM and IgG for *Chlamydia trachomatis* were tested in two separate ELISA kits (Novatec Diagnostica, Germany) using sandwich assay for the qualitative and quantitative determination of antibodies against *C. trachomatis* (This test was performed following the procedure protocol included within the kit packing as issued from the manufacturer company).

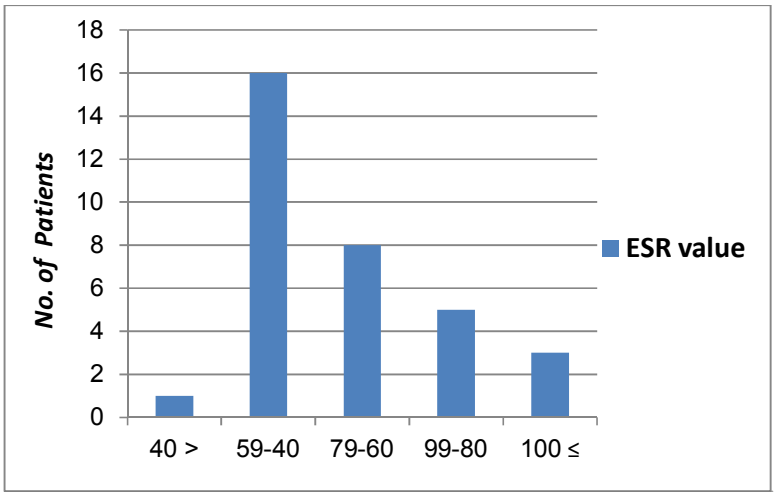


Fig. 2. The distribution of cases according to ESR values

Statistical analysis was done using GraphPad Software, (California, USA). Two samples unpaired T test was used to find the correlation between means of normally continuous samples of two groups of data. Findings with *P* value less than 0.05 were considered significant.

3. RESULTS AND DISCUSSION

The distribution of clinical manifestations among the study group is showed in Table 3. All the chronic arthritis patients were suffering from pain, and the majority (about 97%) were having morning stiffness.

Pain is a very clear complaint and it was annoying symptom to the vast majority of patients in this study, as it is shown in Table 3. Besides, the morning stiffness was also a well defined constitutional symptom in most of these cases. We suppose that it may be either a consequence of pain experienced during moving a joint, the symptom of loss of range of motion or the physical sign of reduced range of motion. Some articles and reports agreed with our finding in the present study [8,16]. The remaining clinical manifestations varied from fever to swelling and extra-synovial ones, that are reported in less percentages compared with the formal two.

The mean *C. trachomatis* IgM levels in sera of current arthritis cases are compared with those of the control group (Table 4). All cases of both groups were giving results below cut off value for the ELISA kit used. Non-significant relation regarding IgM levels was found between both groups in current study.

The mean *C. trachomatis* IgG levels in sera of current arthritis cases are also compared with those of the control group (Table 5). Although no cases were exceeding the cut off value of the ELISA kit used for IgG level in sera, but a significant relation ($P<0.001$) was found when using T- test to compare mean results in the two study groups.

Chlamydial infection causes serious sequelae, one of which is chronic arthritis. Reports indicate that approximately 5% of those with a Chlamydial infection will develop acute arthritis, and about half of these will proceed to chronicity [17]. Intra-articular persistence of viable, although non-culturable, *C. trachomatis* is considered to be the cause of arthritis [18].

In the current cross sectional study, the distribution of cases according to gender (Fig. 1) showed high female: Male ratio (5.6:1). As a probable explanation, this can be due to current cultural and social custom represented in delayed presentation of female cases and medical self-neglect in Iraqi population.

In Table 1, It is clear that more than half of cases (about 57%) were in age between 30 years and 49 years, with mean age of 46 years old. This clarifies the age range at which the patients suffering from chronic arthritis often present. They more often acquire the disease and seek medical consultation during this period. A number of studies [14,19,20] agreed with this finding.

Table 3. The distribution of clinical manifestations among study group cases

Type of the inflammation	Pain and/or tenderness	Fever	Swelling	Morning stiffness	Limitation of movement and/or deformity	Association with extra-synovial manifestations	Total
Arthritis	27(93%)	5(17%)	7(24%)	28(97%)	16(55%)	11(38%)	29(100%)
Enthesitis	4(100%)	0(0%)	0(0%)	4(100%)	2(50%)	1(25%)	4(100%)
Total	31(94%)	5(15%)	7(21%)	32(97%)	18(54%)	12(36%)	33(100%)

Table 4. The mean IgM levels of both groups in current study

Groups of study	Mean IgM Conc. values (NTU)	T- test	Degree of freedom (n-2)	Standard error (SE) of difference	95% confidence interval	*P*- value
Chronic arthritis group	3.648	1.75	64	0.44	-1.64989 to 0.10904	0.08
Control group	4.419					

Table 5. The mean IgG levels of both groups in current study

Groups of study	Mean IgG Conc. values (NTU)	T- test	Degree of freedom (n-2)	Standard error (SE) of difference	95% confidence interval	P- value
Chronic arthritis group	2.678	3.93	64	0.28	0.54275 to 1.66337	0.0002*
Control group	1.575					

** Highly significant*

As an inflammatory process, patients with chronic arthritis usually presented with elevated ESR; an obvious picture in this study (Fig. 2). In this work, we reported that 52% of patients were having ESR value of 40 – 59 mm/hr. Yet, majority of the enrolled patients had high ESR.

Furthermore, in order to maintain the inclusion criteria, we excluded septic arthritis from the studied sample by history, clinical examination, and laboratory investigations (CBP; with no signs of bacterial infection), as well as rheumatoid arthritis (RA) that was excluded by history, clinical examination, along with the negative RF in all samples sera. This exclusion helped in focusing on the disease in question; chronic aseptic arthritis, and facilitated achieving the aim of this study.

Specific serological tests were conducted in this study using ELISA. Both IgM and IgG for *Chlamydia trachomatis* were tested in patients' group and compared to those of the control subjects as well. As IgM levels are concerned (Table 4), the results showed a non significant difference between both groups in current study ($P>0.05$), which means that there is no considerable relation between the chronic arthritis and anti-*Chlamydia trachomatis* IgM levels.

However, Table 5 demonstrates a strong statistically significant difference between the two study samples ($P<0.001$). Although no cases were exceeding the cut off value of the ELISA kit used for IgG, high titers of anti-*Chlamydia trachomatis* IgG were found in the patients' sera. It is clear that the cut off values in the commercially available kits correspond to the values of the population in the country or area of the manufacturer. This work can confirm the relation between the chronic arthritis and anti-*Chlamydia trachomatis* IgG levels. The finding of this work agreed with some studies conducted in chronic arthritis cases [21-23].

4. CONCLUSION

This study showed that there is a significant statistical relationship between chronic arthritis and previous Chlamydia infection (demonstrated by high titer of anti-*Chlamydia trachomatis* IgG) among the patients enrolled in this work.

CONSENT

All authors declare that written informed consent was obtained from each patient before enrolment in this study for publication of this report.

ETHICAL APPROVAL

The study was approved by the Committee of Medical Microbiology Dept./ College of Medicine-Tikrit University for ethical consideration, and informed consent was obtained from all patients. This study is not against the public interest, or that the release of information is allowed by legislation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Inman RD, Chiu B. Synoviocyte-Packaged *Chlamydia trachomatis* induces a chronic aseptic arthritis. J. Clin. Invest. 1998; 102(10):1776-82.
2. Inman RD. Rheumatic disease etiology-environmental factors. In Dieppe P, and Klippel J, editors. Rheumatology. Gower Medical Publishing, London. 1994;14.1-14.6.
3. Schachter J. Infection and disease epidemiology. In Chlamydia: Intracellular Biology, Pathogenesis, and Immunity. Edited by Stephens RS. Washington DC: American Society for Microbiology Press. 1999;139-69.
4. Braun J, Laitko S, Treharne J, et al. Chlamydia pneumoniae—a new causative agent of reactive arthritis and undifferentiated oligoarthritis. Ann Rheum Dis. 1994;53:100–5.
5. Hannu T, Puolakkainen M, Leirisalo-Repo M. Chlamydia pneumonia as a triggering infection in reactive arthritis. Rheumatology (Oxford). 1999;38:411–4.
6. Gerard HC, Branigan PJ, Schumacher HR Jr, et al. Synovial *Chlamydia trachomatis* in patients with reactive arthritis / Reiter's syndrome are viable but show aberrant gene expression. J Rheumatol. 1998; 25:734–42.
7. Gerard HC, Wang Z, Whittum-Hudson JA, et al. Cytokine and chemokine mRNA produced in synovial tissue chronically infected with *Chlamydia trachomatis* and *C. pneumoniae*. J Rheumatol. 2002;29: 1827–35.
8. Kvien TK, Glennas A, Melby K, et al. Reactive arthritis: Incidence, triggering agents and clinical presentation. J Rheumatol. 1994;21(1):115-22.
9. Schumacher HR. Chlamydia-associated arthritis. Isr Med Assoc J. 2000;2:532-35.
10. Poole S, Highton J, Wilkins RJ, et al. A search for Chlamydia trachomatis in synovial fluids from patients with reactive arthritis using the polymerase chain reaction and antigen detection methods. Br J Rheumatol. 1992;31:31-34.
11. Bas S, Griffais R, Kvien TK, et al. Amplification of plasmid and chromosome Chlamydia DNA in synovial fluid of patients with reactive arthritis and undifferentiated seronegative oligoarthropathies. Arthritis Rheum. 1995;38:1005-13.
12. Kuipers JG, Sibilia J, Bas S, et al. Reactive and undifferentiated arthritis in North Africa: Use of PCR for detection of *Chlamydia trachomatis*. Clin Rheumatol. 2009;28:11-16.
13. Siala M, Gdoura R, Younes M, et al. Detection and frequency of *Chlamydia trachomatis* DNA in synovial samples from Tunisian patients with reactive arthritis and undifferentiated oligoarthritis. FEMS Immunol Med Microbiol. 2009;55:178-86.
14. Kumar P, Bhakuni DS, and Rastogi S. Diagnosis of *Chlamydia trachomatis* in patients with reactive arthritis and undifferentiated spondyloarthropath. J Infect Dev Ctries. 2014; 8(5):648-54.
15. Leirisalo-Repo M. Reactive arthritis. Scand J Rheumatol. 2005;34:251.
16. Nakano T and Eto H. Clinical and histopathological presentation of pustular psoriasis in an HLA-B27-positive Caucasian with reactive arthritis. Kitasato Med J. 2011;41:97-102
17. Kvien TK, Glennås A, Melby K, et al. Reactive arthritis: Incidence, triggering agents, and clinical presentation. J Rheumatol. 1994;21:115-22.
18. Hudson AP, Gerard HC, Branigan PJ, et al. Viability of inapparent synovial *Chlamydia trachomatis* in patients with Reiter's syndrome (RS) / reactive arthritis (ReA). Arthritis Rheum. 1995;40:393.
19. Sampaio-Barros PD, Bortoluzzo AB, Conde RA, et al. Undifferentiated spondyloarthritis: A longterm followup. The

Journal of Rheumatology. 2010;37(6): 1195–99.

20. Geirsson AJ, Eyjolfsdottir H, Bjornsdottir G, et al. Prevalence and clinical characteristics of ankylosing spondylitis in Iceland - a nationwide study. Clinical and Experimental Rheumatology. 2010;28(3): 333–40.
21. Bednarek-Skublewska A, Majdan M, Dryglewska M, et al. *Chlamydia trachomatis* infection in chronically hemodialyzed patients. Rocz Akad Med Bialymst. 2005;50:307-10.
22. Keat AC, Thomas BJ, Taylor-Robinson D, et al. Evidence of *Chlamydia trachomatis* infection in sexually acquired reactive arthritis. Ann Rheum Dis. 1980;39(5):431-37.
23. Bas S, Vischer TL. *Chlamydia trachomatis* antibody detection and diagnosis of reactive arthritis. British Journal of Rheumatology. 1998;37:1054–59.

QUESTIONNAIRE

1. The Questionnaire

The Relation Between Chronic Aseptic Arthritis and Previous Chlamydia Infection Among Middle Aged Iraqi Patients

1 of 2

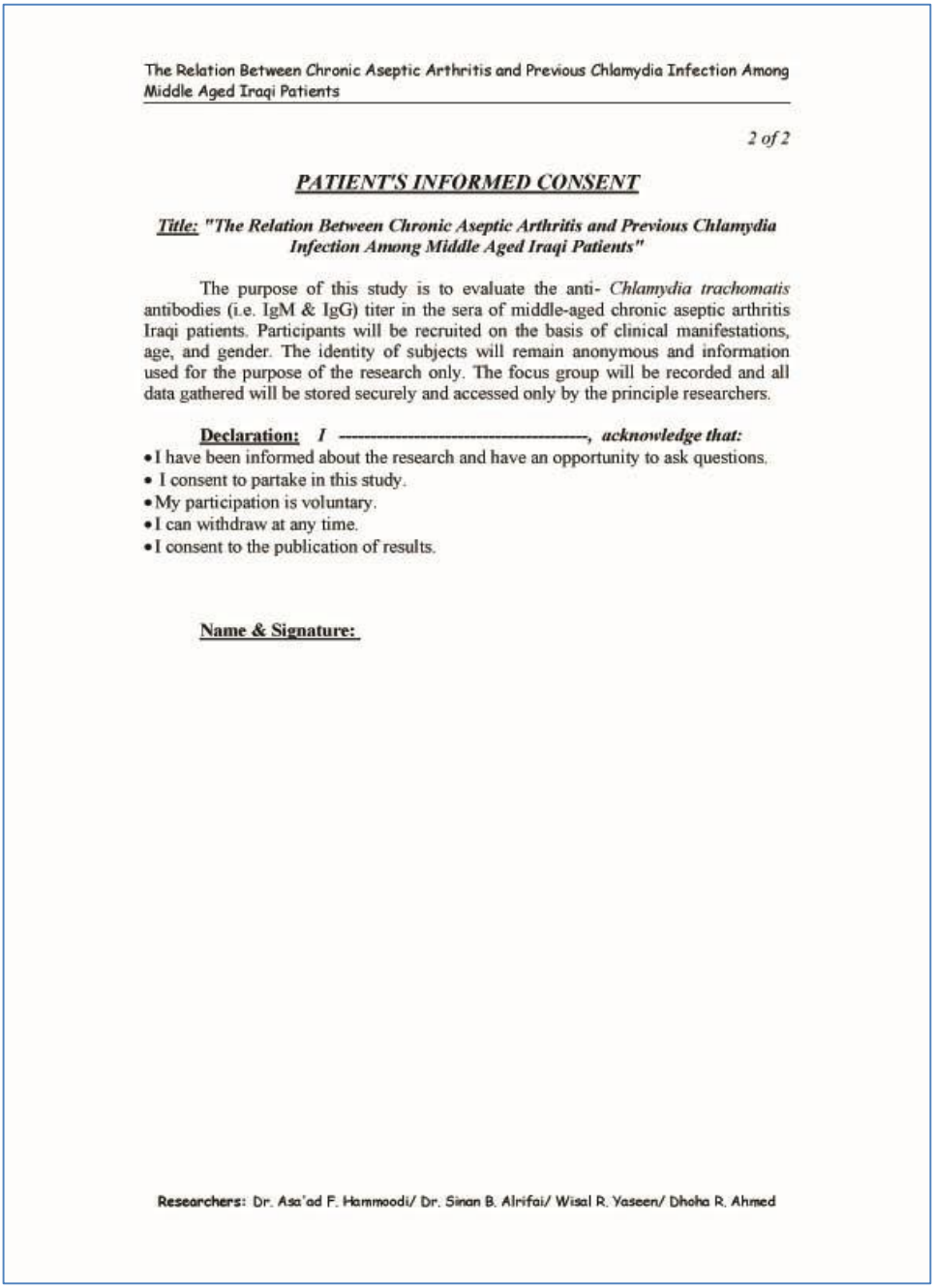
RESEARCH QUESTIONNAIRE

Case No. ( )
Name: ***Age:***
Gender:
Residence: ***Occupation:***

- *Main medical condition(s): 1. Arthritis □ 2. Enthesopathy □ 3. Others □ (Mention:)*
- *Duration of the condition: ( )*
- *No. of joint affection: 1. Mono-arthritis □ 2. Oligo-arthitis □ 3. Poly-arthritis □*
- *Site of joint(s) affected: 1. Upper □ 2. Lower □ 3. Different sites □*
- *Pattern of joint affection: 1. Ascending □ 2. Descending □ 3. Migratory □*
- *Presence of extra-synovial manifestations: 1. No □ 2. Yes □ (Mention:)*
- *Presence of other medical conditions: 1. Hypertension □ 2. Diabetes □ 3. Genitourinary manifestations □ 4. Inflammatory Bowel Diseases □ 5. Cardiac manifestations □ 6. Others □ (Mention:)*
- *General symptoms & signs: 1. Fever □ 2. Pain &/or Tenderness □ 3. Swelling □ 4. Morning Stiffness □ 5. Movement limitation &Deformity □ 6. Others □ (Mention:)*
- *Investigation results:*
  - *RF: 1. Positive □ 2. Negative □*
  - *ESR value: ( )*
  - *CBP: 1. Normal □ 2. Abnormal □ (Mention:)*
  - *IgM concentration: ( ) NTU*
  - *IgG concentration: ( ) NTU*
- *Notes:*

Researchers: Dr. Asa'ad F. Hammoodi/ Dr. Sinan B. Alrifai/ Wisal R. Yaseen/ Dhoha R. Ahmed

2. Patient's Informed Consent



The Relation Between Chronic Aseptic Arthritis and Previous Chlamydia Infection Among Middle Aged Iraqi Patients

2 of 2

PATIENT'S INFORMED CONSENT

***Title:* "The Relation Between Chronic Aseptic Arthritis and Previous Chlamydia Infection Among Middle Aged Iraqi Patients"**

The purpose of this study is to evaluate the anti- *Chlamydia trachomatis* antibodies (i.e. IgM & IgG) titer in the sera of middle-aged chronic aseptic arthritis Iraqi patients. Participants will be recruited on the basis of clinical manifestations, age, and gender. The identity of subjects will remain anonymous and information used for the purpose of the research only. The focus group will be recorded and all data gathered will be stored securely and accessed only by the principle researchers.

Declaration: *I* ----------, ***acknowledge that:***

- I have been informed about the research and have an opportunity to ask questions.
- I consent to partake in this study.
- My participation is voluntary.
- I can withdraw at any time.
- I consent to the publication of results.

Name & Signature:

Researchers: Dr. Asa'ad F. Hammoodi/ Dr. Sinan B. Alrifai/ Wisal R. Yaseen/ Dhoha R. Ahmed

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=1116&id=12&aid=9077