Is there any relationship between toxoplasma infection and reactive arthritis?

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ABSTRACT

Background: The diagnosis of reactive arthritis is a challenging clinical problem in daily practice. Although there are many triggering infectious agents for reactive arthritis, Toxoplasmosis, a worldwide parasitic infection has not been reported. **Aim:** We investigated the serologic evidence of *Toxoplasma gondii* (*T. gondii*) infection in patients with newly diagnosed reactive arthritis after six weeks of the onset of the first symptom but no demonstrable triggering agent for reactive arthritis. **Setting and Design:** Clinical controlled study. **Materials and Methods:** We screened serologically the serum toxoplasma IgM and IgG antibody (Ab) titers which revealed toxoplasma infection in 50 patients with reactive arthritis (40 female, 10 men) and no demonstrable triggering agent and control subjects (32 female, 8 male). **Statistical Analysis:** SPSS 10.0 software package program was used. **Results:** The mean age of the patients and controls was similar (41.3± 12.0 vs. 39.6±11.8 years) respectively. The prevalence of IgG Ab titers of T. gondii in patients and controls were found to be 52% and 47.5%, respectively. Mean serum Toxoplasma IgG Ab levels were found to be 16.5±14.5 IU/ml, and 16.9±13.8 IU/ml in patients and control subjects respectively ($P>0.05$). We did not find any Toxoplasma IgM Ab titer demonstrating the acute or sub-acute infection in the serum of patients or controls. **Conclusion:** Although past Toxoplasma infection was prevalent in both groups, we did not find any subject with acute Toxoplasma infection in patients with newly diagnosed reactive arthritis and healthy controls. Despite the fact that our study group was small, we suggest that *T. gondii* does not seem to be a triggering agent for reactive arthritis and past infection may be a coincidental finding.

KEY WORDS: Reactive arthritis, *Toxoplasma gondii*, toxoplasma IgM and IgG antibodies

Toxoplasmosis is the disease caused by infection with the obligate intracellular parasite *T. gondii* and has worldwide distribution. The most common clinical presentation of acquired Toxoplasmosis is asymptomatic. Only about 10% of infected individuals develop signs and symptoms. Undercooking or insufficient freezing of meat is an important source of infection in the developed world. In Central America, France, Turkey, and Brazil, the seroprevalence is high. *T. gondii* cysts are present in 10-35% of lamb and pork meat and in a much lower percentage of beef.[1, 2] Antibody seropositivity for *T. gondii* in sheep was found to be between 7.1% and 88.7% in different parts of Turkey.[3-5]

In humans, *T. gondii* infection may cause a symmetrical polyarthritis of the small joints of the hands, wrists, and knees in a rheumatoid pattern. All patients have serological evidence of acute Toxoplasma infection.[6-9]

Reactive arthritis is a clinical diagnosis, there being no definitive diagnostic laboratory test or radiographic finding. The diagnosis should be considered in any patient with an acute inflammatory, asymmetric, additive arthritis or tendinitis. The evaluation should include questioning regarding possible triggering events such as an episode of diarrhea or dysuria before the onset of the first arthritic symptom.[10]

See editorial on page no. 2

In this study, we investigated the serological evidence of *T. gondii* in patients with newly diagnosed reactive arthritis and healthy controls to determine the relationship between *T. gondii* infection and reactive arthritis.

Materials and Methods

In this prospective controlled study, our study group consisted of 50 patients (40 women, 10 men) with newly diagnosed reactive arthritis and 40 (32 women, eight men) healthy control subjects admitted to our outpatient clinic of internal medicine between January 2003 and January 2004. In this time period, patients with newly diagnosed reactive arthritis were evaluated for the study. Patients and control subjects were from the same geographic area located at Cukurova region of Southern Turkey.

The control group was chosen from the subjects who did not have any complaint and disease when they came for routine checkup. Exclusion criteria: subjects who had other known disorders, were taking medicine for any reason, smokers, abusers and vegetarians. Also subjects who had pets such as cat, dog or others or who had jobs involving them, and subjects working at a microbiology laboratory were excluded from the study. Written informed consent was taken from patients and controls. The study was approved by the local ethical committee.

Reactive arthritis was diagnosed by detailed history (those subjects who were completely well until six weeks ago and preceding infection one to four weeks before the onset of the first symptom), serologic tests for infection agents, C-reactive protein (CRP), complete blood count (CBC), rheumatoid factor (RF), antinuclear antibody (ANA), and erythrocyte sedimentation rate (ESR), plain X-ray of involved joints and the exclusion of other causes of arthritis such as septic arthritis, crystal-induced arthritis, sarcoidosis, acute rheumatic fever, systemic lupus erythematosus and rheumatoid arthritis. The serologic tests were performed for salmonella, yersinia, campylobacter, chlamydia, neisseria gonorrhoeae, borrelia burgdorferi and beta hemolytic streptococci (antistreptolysin O (ASO) antibody), HIV, Hepatitis A, B, C and CMV infections. Liver (AST, ALT, GGT) and kidney function tests were done. Bacteriological cultures of feces, urine and throat were obtained.

T. gondii infection was screened serologically in patients with negative results for infectious agent on cultures and serologic markers of the triggering agents mentioned above for reactive arthritis.

Serological methods for T. gondii

Serum *T. gondii* IgM and IgG Ab levels were studied by microparticle enzyme immunoassay, AXSYM (Abbott, USA). The serum samples of patients and control subjects were frozen at –20ºC and stored until analysis. Acute *T. gondii* infection was considered in patients who had blood samples with index values for IgM Ab equal to or greater than 0.600 IU/mL. Index values of less than 0.500 are negative for Toxoplasma IgM. Index value results equal to or greater than 0.500 and less than 0.600 are equivocal. Toxoplasma IgG Ab levels greater than or equal to 3IU/mL revealed acute or past toxoplasma infection. Toxoplasma IgG Ab assay titration less than 2IU/mL was assessed as negative.

All statistical analyses were performed using SPSS v.10.0 software (SPSS Inc., Chicago, IL, USA). The descriptive data was given as mean ± standard deviation (SD). The frequencies of parametric and nonparametric descriptive tests of both groups were determined, and compared by unpaired Student-t test, and chi-square tests with a 95% confidence interval. $P<0.05$ was considered as significant.

Results

Mean age and gender were not different in patient and controls (41.3± 12.0 vs. 39.6±11.8 years, and 40/10 vs. 32/8, $P>0.05$), respectively. Of all patients with reactive arthritis, 18 had asymmetrical oligoarthritis of large joints, six asymmetrical sacroileitis, and 26 asymmetrical polyarthritis of small and large joints. Toxoplasma IgM reactivity was not detected either in patients or controls. Seropositivity for Toxoplasma IgG Ab was found in 52% (26/50) of the patients, and 47.5% (19/40) of the controls ($P>0.05$). Mean serum IgG Ab levels were 16.5±14.5 IU/mL, and 16.9±13.8 IU/mL in patients and control subjects, respectively. There was no significant difference between the two groups with respect to serum IgG Ab levels ($P>0.05$).

Discussion

Reactive arthritis is an acute, nonsuppurative, sterile, and inflammatory arthritis following an infection after one to four weeks. The most common microbial pathogens known to induce reactive arthritis are *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*, and *Chlamydia*.[11, 12]

No validated and generally agreed diagnostic criteria exist, but the diagnosis of reactive arthritis is mainly clinical, based on acute oligoarticular arthritis of larger joints that develops within two to four weeks of the preceding infection. In about 25% of patients infection can be asymptomatic. Diagnosis of the triggering infection is very helpful for the diagnosis of reactive arthritis. However, after the onset of arthritis, this is less likely to be possible. Therefore, diagnosis must rely on various serological tests to demonstrate evidence of previous infection, but these serological tests are unfortunately not standardized.[10] Likewise, in our patients, we could not find any triggering agents or positive serologic markers of antecedent infection. This situation is not uncommon in general clinical practice. Therefore, we screened *T. gondii* infection, to find whether it is a triggering agent for reactive arthritis.

There are reports of rheumatic disorders associated with *T. gondii*. Asymmetrical polyarthritis has been reported to develop in patients infected with *T. gondii*. Rheumatoid factor, also an acute phase reactant, may or may not be present in serum, but all patients have serological evidence of acute Toxoplasma infection.[6-9]

Diagnosis of Toxoplasmosis can be achieved by demonstrating the parasite in biological samples or by detection of specific antibodies. Molecular diagnosis by PCR has reduced greatly the time required to determine the presence of parasites when compared with the time required following mouse or tissue culture inoculation. Real-time PCR and other gene targets will probably be used in the future, but serological tests to determine specific antibodies are currently the first-line method of diagnosis for current, recent or past infection.[13] The diagnosis of acute *T. gondii* infection can be established by detection of the simultaneous presence of serum Toxoplasma IgM and IgG Ab by ELISA.[14, 15] Toxoplasma IgM Abs appear earlier than IgG, and may remain positive for more than 12 months after the onset.[16]

In this study, past *T. gondii* infection among patients with newly diagnosed reactive arthritis and healthy control subjects was

found in about 50% of the cases, however, seropositivity for Toxoplasma IgM Ab titration revealing acute infection was not found. Comparisons of the frequency of IgG Ab positivity and IgG levels of the patients with those of the healthy asymptomatic controls (52% vs. 47.5%) showed no significant difference between them. In certain studies performed in our country, seroprevalences of *T. gondii* infection were found to be between 19.2 and 85%.[17,18] In a cross-sectional study from Aydin province in Turkey, among the pregnant women, the seroprevalence of anti-Toxoplasma IgG Ab for Toxoplasmosis was found to be 30.1%. Furthermore, they found no significant relation between Toxoplasma IgG Ab levels and education level, being native or immigrant, abortion history, consumption of meat, vegetable and milk/milk products, personal or kitchen hygiene habits, cat as a pet at home of the pregnant women. They also did not find Toxoplasma IgM Ab, similarly as in our study.

It has been reported that about 50% of the European population has become infected by the third decade of life, and in France this proportion has been close to 80%.[1,2] The prevalence of Toxoplasma seropositivity in the present study was found to be about 50% which is similar to certain European countries and other parts of Turkey.

Conclusion

The incidence of past *T. gondii* infection in the study was found to be as high as the other studies performed in Turkey and Europe. However, we did not encounter any subject with acute Toxoplasma infection among patients with newly diagnosed reactive arthritis and healthy controls. Although our study group is small, we suggest that it seems there is no role of *T. gondii* infection in the occurrence of reactive arthritis, and past infection may be a coincidental finding. Further studies are needed to determine this issue.

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