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# *Arthritis in children as a result of a previous infection caused by Yersinia enterocolitica and Yersinia pseudotuberculosis*

Infections caused by *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*, often referred to as *Yersiniosis*, are classified as diseases occurring in human and animals which originate from their reservoir in a natural environment (sapronosis). Infection occurs orally by contaminated food or water. *Y. pseudotuberculosis* and *Y. enterocolitica* are gram-negative, rod-shaped bacterias of the genus *Yersinia*, belonging to the family of *Enterobacteriaceae*. They are enteric pathogens, responsible for triggering a large number of different symptoms ranging from diarrhea and abdominal pain, to more systemic ones such as fever or scarlatinform skinrash. Others may include myocarditis, Crohn's disease, Reiter's syndrome, chronic pancreatitis, ankylosing spondylitis, acute interstitial nephritis, Kawasaki syndrome, conjunctivitis, erythema nodosum, lymphadenopathy (1) and arthritis (2. 3).

Reactive arthritis develops 1–4 weeks after gastrointestinal or urogenital infections caused by *Yersinia*. The finding of LPS structures of *Yersinia* in the synovial fluid of human joints is widely regarded to be of paramount importance in the pathogenesis of arthritis (4–6).

Studies suggest that a superantigen YPM, which is produced *in vivo* by *Yersinia*, is responsible for the induction of IgG synthesis in infected patients. Significantly higher antibody level in the patients with systemic symptoms and the presence of YPM-responsive cells in their lymph nodes suggest that this superantigen may have a key role in the disease process (1).

Owing to the wide diversity of symptoms, *Yersinia*-associated arthritis can pose a complicated diagnostic problem and suggest a rheumatic origin of the disease. In that case, due to the impossibility of isolating the microorganisms at this stage of infection, the basis for the confirmation of diagnosis is the measurement of specific antibody levels against antigen O of *Y. enterocolitica* and *Y. pseudotuberculosis* (7, 8).

The aim of the study was to determine the relationship between symptoms of arthritis and infections caused by *Y. enterocolitica* and *Y. pseudotuberculosis* in children.

## MATERIAL AND METHODS

Blood samples of 68 randomly chosen patients from the Pulmunology and Reumatology Ward, Children Hospital of Lublin, Poland, were examined for the presence of antibodies against *Yersiniae*. A group of 17 children patients with the highest levels of immunoglobulins IgA, IgM and IgG against *Yersinia* was consequently chosen and carefully studied. A broad array of different clinical

complications which appeared in children infected with *Yersinia* was then taken into consideration.

In order to indicate the level of anti-*Yersinia* antibodies in human plasma, a quantitative *in vitro* test based on the principle of an indirect sandwich ELISA-recomWell Yersinia IgM, IgG, IgA (MICROGEN) was used. This procedure involves using *Yersinia* outer membrane proteins that are produced by genetic engineering techniques. In this way only antibodies against *Y. pseudotuberculosis* and *Y. enterocolitica* antigens are detected. The antibody levels in units per ml were assigned to the extinction values using a formula. U/ml = (extinction sample/extinction cutoff) x 20 (positive test result : U/ml >24; negative test : U/ml <20).

For the purpose of an *in vitro* quantitative determination of C-Reactive-Protein concentration in the plasma, a latex-enhanced turbidimetric method was used (normal range of levels for the children over the age of one week: CRP< 0.5 mg/dl).

C-Reactive-Protein is an acute phase reactant found at low concentrations in the plasma of normal patients. However, during the acute stage of an inflammatory reaction, CRP levels are elevated significantly making it an excellent early indicator of an infection. Furthermore, C-Reactive-Protein can serve as a marker in non-infectious inflammatory diseases, such as reactive arthritis. Levels of CRP concentration may inform of the activity of inflammatory processes in these cases.

## RESULTS

As it is presented below (Table 1) all of the 17 patients were afflicted with either reactive arthritis or other diseases with rheumatic origin, which is a common outcome of autoimmunological processes triggered by *Yersinia*.

Table 1. Diseases affecting the studied group of 17 children

| No. patients | Age (years) | Sex F – female M – male | Disease | Level of antibodies against *Yersiniae* (U/ml) | | | CRP (mg/dl) |
|---|---|---|---|---|---|---|---|
| | | | | IgM | IgA | IgG | |
| 1 | 10 | M | Reactive arthritis | 21.30 | 11.90 | 32.10 | 0.50 |
| 2 | 15 | M | Reactive arthritis | 18.60 | 9.10 | 51.00 | <0.50 |
| 3 | 7 | F | Connective tissue inflam.Uveitis | 12.70 | 11.20 | 29.80 | <0.50 |
| 4 | 12 | M | Reactive arthritis | 20.90 | 65.20 | 63.90 | <0.50 |
| 5 | 10 | F | Idiopathic arthritis of the youth | 9.80 | 15.10 | 34.70 | <0.50 |
| 6 | 15 | F | Reactive arthritis | 25.60 | 13.90 | 22.40 | <0.50 |
| 7 | 5 | F | Shonlein-Henoch disease | 7.00 | 15.90 | 29.70 | <0.50 |
| 8 | 15 | F | Idiopathic arthritis of the youth | 7.90 | 12.20 | 74.90 | 5.39 |
| 9 | 6 | M | Connective tissue inflammation | 101.90 | 43.20 | 242.60 | <0.50 |
| 10 | 15 | F | Pain in the Achilles tendon | 6.00 | 10.80 | 56.00 | - |
| 11 | 8 | F | Reactive arthritis | 9.30 | 7.80 | 32.80 | <0.50 |
| 12 | 9 | F | Reactive arthritis | 7.00 | 16.40 | 164.00 | <0.50 |
| 13 | 12 | F | Reactive arthritis | 9.00 | 8.60 | 34.10 | 21.05 |
| 14 | 5 | M | Idiopathic fever | 11.50 | 8.70 | 36.60 | 2.37 |
| 15 | 14 | M | Reactive arthritis | 11.33 | 19.00 | 209.40 | 0.98 |
| 16 | 7 | M | Reactive arthritis | 8.70 | 8.70 | 33.04 | 1.39 |
| 17 | 12 | F | *Erythema nodosum* | 8.40 | 27.40 | 207.10 | <0.50 |

Reactive arthritisis was the most frequent complication in the studied group (nine cases). Other forms of autoimmunological processes found include idiopathic arthritis of the youth (two cases), connective tissue inflammation (two cases), Shonlein-Henoch disease (one case) and erythema nodosum (one case). In two cases the symptoms were non-specific (pain in the Achilles tendon and idiopathic fever).

Although the clinical symptoms were present in all the children, only five of the17 tested showed an increased C Reactive Protein (CRP) level, which indicated a high level of activity of the inflammatory processes. Patients with normal CRP levels in the plasma were subjected to an intensive anti-inflammatory treatment scheme, which led to the decrease of CRP levels. Nevertheless, it should be noted that even in known cases of inflammatory diseases, normal CRP levels are also possible and cannot be considered as indicators of no inflammation. The increase of the antibody levels was observed most clearly in the IgG class.

## DISCUSSION

Earlier studies conducted by scientists from the Turku University, Finland (6, 9) demonstrated the existence of *Yersinia* LPS in synovial samples of patients with *Yersinia*-triggered reactive arthritis several weeks, and in a few cases even years, after the original infection.It has been also proved that the *Yersinia*-induced arthritis is closely associated with the presence of HLA-B27 (10). Other results (9, 11) show that phagocitosis of *Yersinia enterocolitica* serotype O:3 changes the expression of serological HLA-B27 epitopes on human leukocytes. This is mainly due to the reduced synthesis of HLA-B27 molecules. Down-regulation of epitopes important for the T-cell recognition may impair the elimination of arthritis-triggering bacteria strains and lead to a persistent infection. Furthermore, *Yersinia enterocolitica* seems not only to diminish but also to alter the peptides presented by the HLA-B27 molecules, which may play an important role in the pathogenesis of inducing the autoimmunological mechanisms. This can lead to the development of the reactive arthritis but in the same way provoke connective tissue inflammation, reactive uveitis, Schonlein-Henoch disease, erythema nodosum and idiopathic fever, which have been identified in our group of the 17 patients. The autoimmunological background of these diseases triggered most probably by *Yersinia* cannot be excluded, which refers to the case of the Grave's disease as well (12–14).

## CONCLUSIONS

The study demonstrated the occurrence of *Yersinia*-associated arthritis among children. This form of infection may manifest itself with different symptoms, depending upon the patients' age and immunity. A large group of disorders, triggered by *Yersinia enterocolitica* and *Y. pseudotuberculosis* infection, may be connected with the process of modifying the structure of HLA-B27 epitopes by the bacteria strains, which consequently provokes autoimmunological reactions affecting a wide range of human structures and tissues – including the articulations. What is more, as it has been described above, even a long period of time may pass until the symptoms of reactive arthritis appear. Considering these far-reaching complications, appropriate casual treatment of the bacterial infections ought to be regarded as a major way of preventing their rheumatic consequences. Complicated as it may seem, reasonable attitude should involve scrutinizing minutely all the possible reasons for reactive arthritis, including serological tests for detecting *Yersinia*, role of which has been revealed in the study above.

## REFERENCES


1. Abe J., Onimaru M. et al.: Clinical role for a superantigen in *Yersinia pseudotuberculosis* infection. J. Clin. Invest. 99 (8), 1823, 1997.
2. Sibilia J., Limbach F. X.: Reactive arthritis or chronic infectious arthritis? Ann. Reum. Dis. 61, 580, 2002.
3. Hannu T., Mattila L. et al.: Reactive arthritis after an outbreak of *Yersinia pseudotuberculosis* serotype O:3 infection. Ann. Rheum. Dis., 62, 866, 2003.
4. Hammer M., Zeidler H. et al.: *Yersinia enterocolitica* in the synovial membrane of patients with *Yersinia*-induced arthritis. Arthritis Reum., 33 (12), 1795, 1990.
5. Wuorela M., Jalkanem S. et al.: *Yersinia* lipopolysaccharide is modified by human monocytes. Infect. Immun., 61 (12), 5261, 1993.
6. Granfors K., Jalkanen S. et al.: *Yersinia* antigens in synovial-fluid cells from patients with reactive arthritis. N. Engl. J. Med., 320 (4), 216, 1989.
7. Silva E. E., Ramos O. P. et al.: *Yersinia enterocolitica* O:3 isolated from patients with or without reactive arthritis induces polyclonal activation of B cells and autoantibody production *in vivo*. Autoimmunity, 36 (5), 261, 2003.
8. Granfors K., Viljanen M. et al.: Persistence of IgM, IgG, and IgA antibodies to *Yersinia* in *yersinia* arthritis. J. Infect. Dis., 141 (4), 424, 1980.
9. Wuorela M., Jalkanen S. et al.: *Yersinia enterocolitica* serotype O:3 alters the expression of serologic HLA-B27 epitopes on human monocytes. Infect. Immun., 65 (6), 2060, 1997.
10. Falgarone G., Blanchard H. S. et al.: Cytotoxic T-cell-mediated response against *Yersinia pseudotuberculosis* in HLA-B27 transgenic rat. Infect. Immun., 67 (8), 3773, 1999.
11. Saxena N., Misra R., Aggarwal A.: Is the enthesitis-related arthritis subtype of juvenile idiopathic arthritis a form of chronic reactive arthritis? Rheumatology (Oxford), 45 (9), 1129, 2006.
12. Shenkman L., Bottone E. J.: Antibodies to *Yersinia enterocolitica* in thyroid disease. Ann. Intern. Med., 85 (6), 735, 1976.
13. Hannu T., Inman R. et al.: Reactive arthritis or post-infection arthritis ? Best. Pract. Res. Clin. Rheumatol., 20 (3), 419, 2006.
14. Hill Gaston J. S., Lillicrap M. S.: Arthritis associated with enteric infection. Best. Pract. Res. Clin. Rheumatol., 17 (2), 219, 2003.


## SUMMARY


Infections caused by *Yersinia enterocolitica* and *Y. pseudotuberculosis* are classified as diseases which originate from their reservoir in a natural environment (sapronosis). *Yersiniosis* may manifest itself in a wide range of different clinical forms – including arthritis. Due to the impossibility of isolating the microorganisms, credible confirmation of the diagnosis requires indicating the level of specific antibodies against *Yersinia*. The aim of the study was to determine the relationship between symptoms of arthritis and infections caused by *Yersinia* in children. Levels of specific antibodies were determined in the plasma of the children afflicted with arthritis. As a result, the study revealed a large number of *Yersinia*-associated arthritis cases, treatment of which should undoubtedly involve considering a bacterial pathogenesis of the disease and its autoimmunological background.

Zapalenie stawów u dzieci jako efekt wcześniejszej infekcji bakteriami *Yersinia enterocolitica* i *Yersinia pseudotuberculosis*

Infekcje spowodowane przez *Yersinia enterocolitica* i *Y. pseudotuberculosis* są klasyfikowane jako choroby wywodzące się z ich rezerwuaru w środowisku naturalnym (sapronozy). Yersinioza może manifestować się poprzez szeroki zakres różnych klinicznych form, obejmujących zapalenie stawów. Z powodu braku możliwości wyizolowania mikroorganizmów wiarygodne potwierdzenie diagnozy wymaga oznaczania poziomu specyficznych przeciwciał anty-*Yersinia*. Celem badania było określenie związku między objawami zapalenia stawów a infekcjami spowodowanymi przez *Yersinia* u dzieci. Określono poziomy przeciwciał w surowicy dzieci dotkniętych zapaleniem stawów. W rezultacie badanie ukazało dużą liczbę przypadków zapalenia stawów związanych z infekcjami *Yersinia*, których leczenie powinno niewątpliwie obejmować rozważenie bakteryjnej patogenezy choroby i jej autoimmunologicznego podłoża.