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Ocular Symptoms (Conjunctivitis, Uveitis) in Reactive Arthritis

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1. Introduction

The reactive arthritis (ReA) is an autoimmune disorder usually induced by the prior infection. Conjunctivitis, urethritis and arthritis emerging after the prior onset of diarrhea were first described by Stoll in 1776. In 1818, Benjamin Brodie described 5 cases of conjunctivitis, urethritis and arthritis with a history of venereal diseases. In 1916, Fiessinger and Leroy described 4 patients with an oculo-urethro-synovial syndrome following a diarrhea caused by Shigella. In the same year, Hans Reiter described a triad of symptoms: nongonococcal urethritis, conjunctivitis and arthritis suffered by a young officer with bloody diarrhea and linked these symptoms to the Treponema infection. Until modern times, many researchers used the term Reiter's syndrome for this triad of symptoms. In 1969, the use of the term reactive arthritis (ReA) was proposed, and in 1977, following the disclosure of the war crimes committed by Hans Reiter, it was recommended not to use the name of Reiter's syndrome due to ethical reasons. Based on the analysis of the literature the proportion of authors who use Reiter's name to describe the syndrome has decreased from 34% in 1998 to 18% in 2003 and to 9% in 2007 (Keyan & Rimar, 2008).
Reactive arthritis belongs to a group of diseases known as autoimmune seronegative spondyloarthropathy that is associated with a high incidence of HLA antigen B 27. Reactive arthritis is a disease with diverse clinical manifestations affecting the peripheral joints, spine, skin, eyes, digestive and other systems. The variety of symptoms means that patients, especially in the initial stage of the disease, are treated by the specialists of other fields than rheumatology.

2. Definition

The reactive arthritis is an asymmetric, non septic inflammation of several joints, mainly of the lower limbs, associated with the occurrence of a change called "enthesitis" (inflammation of the tendon), preceded by an extraarticular manifestation and by a documented infection (with or without symptoms present) with: Salmonella, Campylobacter, Yersinia, Shigella flexneri, Chlamydia trachomatis, Chlamydia pneumoniae; rarely with: Clostridium difficile, Mycobacterium bovis BCG, Mycoplasma species (e.g. Ureoplasma urealyticum), and very rarely with: Giardia Cryptospotidium, Shigella sonnei, Chlamydia psitacci, Hafnia alvei, Vibrio parahaemolyticus or other microorganisms. The reactive arthritis often has an acute onset. ReA may also take an atypical course, as inflammation can affect a single joint only,

with the concurrent presence of classic symptoms preceded by the diarrhea or urethritis / cervicitis with no infection detected.

3. Pathogenesis

The key role in the pathogenesis of reactive arthritis is assigned to the presence of bacteria or their products in the joint structures and the local immune response to the bacterial antigens. The presence of Chlamydia trachomatis has been demonstrated not only in reactive arthritis, but also in the synovial fluid of approximately 30% of patients with undifferentiated arthritis of few joints (the same situation takes place in the case of Chlamydia pneumoniae). In the case of Enterobacteriaceae (with the exception of Campylobacter jejuni and Yersinia) PCR (Polymerase Chain Reaction) testing often reveals DNA of these bacteria in the articular structures, while the ribosomal RNA is detected in Yersinia infections. The Yersinia penetrate into the M cells of the Peyer's patches, where the reaction between the invasive bacterial proteins and integrin SS1 takes place. Yersinia can be transferred by phagocytes through the mucosal barrier and enters into the joint via blood pathway. The lymph nodes may constitute a reservoir of live Yersinia bacteria for many months following the manifestation of the first symptoms of reactive arthritis, which leads to a high level of long-lasting antibodies against these bacteria, while only bacteria fragments are detected in the joints.

The emergence of reactive arthritis following the infection with Yersinia can be attributed to the presence of the bacteria derived arthritogenic peptide, which epitope is presented to T-cells by the phagocytes in the synovial tissue. The HLA B27 + T cells respond to the 60kDa heat shock protein epitope and beta-subunit of the Yersinia's urease, which can be detected in the joint. The Yersinia infection may be persistent in the lymph nodes or in the mucosa and the bacteria can be transported to the joint by the monocytes (Gaston et al. 1999). A similar mechanism applies to the development of reactive arthritis induced by Salmonella, in which the persistent presence of the bacterial lipopolysaccharide (LPS) in the synovium has been demonstrated.

In the case of Chlamydia trachomatis, which is an intracellular pathogen, the epithelial cells are the primary location of the bacterial colonization. Chlamydia trachomatis can later infect other types of cells such as macrophages and other phagocytic cells.

A replication of Chlamydia trachomatis in monocytes leads to the recognition of the Chlamydia antigen and induces the process of complex forming with class I and II HLA antigens that are presented on the CD4+ and CD 8+ T cells. The persistence of Chlamydia trachomatis can be long standing, as it is confirmed by the presence of bacterial mRNA, rRNA and DNA (PCR detected) in the synovium and in the peripheral blood (Gerard et al.1998, Kuipers et al., 1998, Zeidler et al.2004). The persistence of the infection is probably aided by the state of imbalance between cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10) – this imbalance being confirmed in vivo. Th1 cytokines such as: interleukin-12 (IL-12), interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) participate in the elimination of bacteria. The reduction of the activity of these cytokines or increase in Th2/Th3 cytokine production (especially of IL-10) reduces the capability of bacteria elimination from the organism. In patients with persistent infection high levels of IL-10 in the intestine, urogenital and respiratory systems has been demonstrated (Yin et al.1997).

IL-6, IL-1 beta and IL-17 and IL-21 (Singh et al. 2011) play the key role in the formation of synovitis in ReA.

An important role in the pathogenesis of reactive arthritis and other spondyloartroaties is assigned to HLA B27 antigen. According to the arthritogenic peptide theory, it is believed that certain subtypes of HLA-B27 containing unique amino acid may be associated with the bacterial arthritogenic peptide and can be recognized by CD8 + T cells. This causes the response to the bacterial peptide, autoreactivity of T lymphocytes which recognize this peptide similar to the host's and activated by the host's peptides in the joints. HLA-B 27 antigens are present in high proportion of patients with ReA induced by: Shigella (80-90%) Yersinia (70-80%), Chlamydia (40-50%) and Salmonella (20-33%) (Nicholis 1975). According to the recently most popular ReA pathogenesis model, called "multi-hit theory" the activation of the immune response in the reactive arthritis and other spondyloartropathies is a result of many circumstances such as: the effect of bacterial arthritogenic products (including lipopolisaccharides), HLA B-27 antigen presence, the extension of bacteria elimination time and other genetic or biomechanical factors. It was also reported that there is a link between HLA B 51 antigen, not only with the Behcet's disease, but also with the ReA - in particular in Japanese population (Shimamoto et all 2000). In HLA B 27 antigen negative patients the presence of HLA B 7, Bw22,B40,B42, B60 antigens – cross-reactive with HLA B27 antigen - may be also found.

4. Clinical symptoms

4.1 The beginning of the disease

The onset is preceded by the symptoms of infection manifesting themselves approximately 4 weeks before the articular symptoms. In the case of Chlamydia trachomatis and Chlamydia pneumoniae the symptoms of infection can go unnoticed, since 70% of infections may be asymptomatic or proceed with minor symptoms only. Infection caused by Chlamydia trachomatis is characterized by the onset of disuric symptoms, urethritis, prostatitis in men and cervitis and / or adnexitis in women. Chlamydia pneumoniae infections usually lead to symptoms of upper respiratory tract infection, cough, pharyngitis, otitis media and sinusitis. In patients infected with Enterobacteriacae e.g Shigella a short episode of joint symptoms may precede the diarrhea. The abdominal pain in the case of Yersinia may be periodically recurrent with enlargement of abdominal lymph nodes and, in some cases, proceeds with appendicitis symptoms. As reactive arthritis is a systemic disease, it may manifest itself with the systemic illness symptoms such as malaise, weakness and fever.

4.2 Symptoms of the musculoskeletal system

Joint symptoms may vary, ranging from arthralgia to the severe inflammation of several joints. Typically inflammation of a single or asymmetric inflammation of several joints is observed. Most commonly the lower extremities joints, such as knees, ankle and foot joints are affected. Inflammation can affect the fingers (dactilitis). This condition is known as „sausage digit" and is attributed to the inflammatory changes in the articular capsule, tendon sheath, periarticular structures and periosteum of the bone. Inflammation of the sacroiliac or spine joints occurs in approximately 50% of patients, manifesting itself as an inflammatory back pain (IBP) with back stiffness and buttock pain. Recurrent arthritis occurs in about 15% of patients and affects mainly patients with reactive arthritis with a history of Chlamydia infection. Inflammation of the tendon (enthesitis) is a common symptom of reactive arthritis. Very characteristic and helpful in identifying the enthesitis

are changes involving the attachments of the bottom surface of the calcaneus, Achilles tendon and plantar attachments - resulting in heel pain and difficulty in walking.

4.3 Changes in skin and mucosa

Inflammation of the mucous membrane of the urogenital tract manifests through the symptoms of urethritis /cystitis and cervitis/ colpitis. In some patients changes may involve the genitals beginning with the vesicular lesions evolving into erosion lesions or macular lesions. These affect the external opening of the urethra, glans and shaft of the penis and may precede joint symptoms. The described changes are referred to as ”balanitis circinata" (serpiginous annular dermatitis of the penis). These changes are painless unless subject to secondary infection and after treatment and recovery leave no scars. In women annular changes in the external genital organs are rare and are called “circinate vulvitis”.

In reactive arthritis, various changes in the oral cavity may appear, such as painless, shiny aphthae on the palate, tongue or on the mucosa of the cheeks and mouth. Delicate red spots may also rarely occur in the palatal tonsils and lingula. Skin lesions in the course of reactive arthritis may be characteristic of this disease and are referred to as "keratoderma blenorrhagica." There are characteristic maculopapular scaly patches with excessive keratosis occurring on the plantar skin of the feet. They may also appear on the big toe, toes and hands. They appear less commonly on the scrotum, penis, trunk and scalp. Histologically, these changes are identical to psoriatic. Often changes called "palmoplantaris pustulosis"(pustular inflammation of the planta and hands) are observed occurring on the plantar side of hands and feet. Changes in nails occur mainly in chronic reactive arthritis, as yellowish or gray discoloration of the nails, bumps, hollow lines and nail keratosis are observed. “Thimble-pitting” of the nails, characteristic of psoriasis, is rarely observed.

Although erythema nodosum often occurs post Yersinia infection, it is not associated with the course of reactive arthritis and has no connection with the presence of HLA-B27 antigen.

4.4 Symptoms concerning the urogenital tract

In addition to the above described inflammatory changes affecting the mucous membrane of the urogenital tract and the skin of sex organs, pathologies of the urinary system in course of ReA may include prostatitis, testitis and / or epididymitis in men and cervicitis and adnexitis in women (both being often asymptomatic in women and diagnosed incidentally during a pelvic gynecological control). Proteinuria caused by IgA nephropathy and amyloidosis due to chronic ReA may also occur, as well as cases of microhaematuria. Pyuria is observed in patients with sexually acquired reactive arthritis (SARA) mainly and occurs usually in Chlamydia trachomatis infections (42-69% of SARA cases), but also in Ureaplasma urealiticum, Gardnerella vaginalis and rarely in recurrent E. coli infections.

Symptoms associated with urinary tract are usually asymptomatic.

4.5 Ocular changes

Uveitis	Scleritis	Conjuntivitis
Common - mainly anterior (AU)	Rare	Keratitis; rare

Table 1. Eye involvement in reactive arthritis.

4.5.1 Conjunctivitis

Conjunctivitis can occur in all types of reactive arthritis, often as an early symptom. It is predominant pathology of the sight organ in reactive arthritis and especially in patients with reactive arthritis caused by Chlamydia. Conjunctivitis affects 1 in 3 patients with ReA caused by Chlamydia, but it can also be observed in reactive arthritis resulting from Enterobacteriacae infection (usually post Shigella, Salmonella and Campylobacter infections, while only in 10% of Yersinia cases patients suffer from conjunctivitis). Symptoms can be bilateral, mild and progressive. In Chlamydia trachomatis induced reactive arthritis conjunctivitis occurs within a few days of the first symptoms of urethritis and usually withdraws within a week. Conjunctivitis can relapse and take a severe course. Conjunctivitis is often painless and non-septic, but it may also cause burning sensation and irritation of the eyes. In the initial period of ReA conjunctivitis is observed in 2% of patients and in 96% patients with the chronic ReA.

4.5.2 Uveitis

In 10 to 20% of reactive arthritis patients with the HLA-B27 antigen present, one or more episodes of acute anterior uveitis occur. The main symptoms present are unilateral eye pain with redness, lacrimation, photophobia, and blurred vision. 13% of patients hospitalized in ophthalmology departments due to uveitis reveal spondyloarthropathies, with 7.2% diagnosed with reactive arthritis and 5.5% with ankylosing spondylitis.
There are case reports of posterior uveitis involving choroid and retina in ReA. The macular degeneration of retina was also described in literature as emerging during post-dysenteria reactive arthritis (Sawhney, Parihar 2006).
Scleritis is rare in patients with ReA but most common in other rheumatic diseases like rheumatoid arthritis.

Anterior uveitis Iritis/irydocyclitis	Intermediate uveitis Vitreous humor	Posterior uveitis Choroid and retina
Acute, unilateral	Incidous onset,unilateral or bilateral	Incidous onset
red eye, pain , photophobia, visual loss (macular oedema)	floaters, haziness of vision	floaters, blurred vision, scotomata, visual loss

Table 2. comparison of uveitis symptoms

In chronic ReA with recurrent ocular symptoms anterior uveitis (92%) and posterior uveitis (64%) are frequently observed, as well as other ocular changes, such as keratitis (64%), cataract (56%), intermediate uveitis (40%), scleritis (28%), cystoid macular edema (28%), papillitis (16%) and glaucoma (16%) (Kiss et al.2003).

4.6 Other symptoms

Inflammatory changes in the aortic arch and ascending aorta and aortic valve regurgitation may also appear (Deer et al. 1991).

5. Morphological changes

5.1 Morphological changes in the joints

The main change which occurs in the joints of reactive arthritis patients is an inflammation of the synovial tissue and presence of inflammatory fluid, leading to the

reduction of complement level in the joint due to local utilization of the complement. In the histological assessment the picture of the inflamed synovium is uncharacteristic and similar to other rheumatic diseases with synovitis. The microscopic examination reveals swelling, vascular lesions with infiltration of lymphocytes and granulocytes as well as plasma cells. In reactive arthritis, in contrast to the synovitis in rheumatoid arthritis, the emergence of pannus rarely takes place. The destructive changes of the bone are unspecific and occur only in patients with chronic inflammatory process. Another characteristic feature of reactive arthritis (as well as of other spondyloartropaties) is the infiltration of macrophages and lymphocytes in ligament trailers and bone tendons (enthesitis), bone resorption and its remodeling, resulting in subchondral hyperostosis and subperiosteal bone formation.

5.2 Morphological changes in the skin and mucous membranes

The skin lesions show infiltration of inflammatory cells such as lymphocytes and plasma cells, causing abnormal thickening and keratinization of the horny layer (stratum corneum), similar to psoriasis. The mucosal changes in the urogenital tract are similar, but keratosis is not observed.

5.3 Morphological changes in the organ of sight

In rheumatic diseases all anatomical parts of eye can be involved. In ReA conjunctiva , iris and cilliary body or both (anterior uveitis), vitreus body (intermediate uveitis), choroid and retina (posterior uveitis) are most commonly affected. ReA rarely concerns sclera (scleritis). In some cases of ReA panuveitis occurs. Changes in the eyes in the course of conjunctivitis are typical of follicular conjunctivitis and occur mainly in infection caused by Chlamydia, Salmonella, Shigella, Campylobacter and Yersinia. In Chlamydia infection , in case of direct autoinfections from the genitourinary tract, typical changes of yellow-white papules (trachoma) frequently occur. Such changes are present in spite of Chlamydia trachomatis serotypes D-K being involved in the pathogenesis of ReA and not serotypes A-C responsible for trachoma forming. Recently, the contribution of Chlamydia trachomatis A-C serotypes to the pathogenesis of ReA with coexisting ocular symptoms has been demonstrated (Gerard et al.2010) as well as the simultaneous presence of chronic inflammatory changes in other tissues and organs.

The histopathology assessment reveals the presence of the chronic inflammation cells localized in submucosal layer, with the predominance of lymphocytes. In addition, extensive fibrynogen deposits in the basal membrane of conjunctiva, infiltration of lymphocytes and macrophages around small blood vessels and lymphocytic infiltrate of the larger vessel walls of conjunctiva have been observed (Purcell & Tsai et al. 1982).

In reactive arthritis, as in other spondyloarthropaties, anterior uveitis occurs. The incidence of anterior uveitis is more common than intermediate or posterior uveitis in ReA patients. The uveitis is more frequent in cases with HLA A-9 and HLA B 40 antigen presence than in cases in which HLA B 27 antigen is present.

Pathomechanism of anterior uveitis development involves humoral and cellular response to retinal antigens (S-antigen) and to interphotoreceptor retinoid binding protein (IRBP) (De Smet et al. 1990). IRBP has been shown to induce posterior uveitis.

The eye is considered as immunologically privileged organ. Some portions of the eye are avascular, and an immunosuppressive factors (such as TGF ß) are present in ocular fluids. In

some cases deviated regulation of the cellular response to the exogenous antigen in anterior chamber of the eye (anterior chamber associated immune deviation- ACAID) occurs. In ACAID phenomenon Ts lymphocytes impair the delayed hypersensitivity and complement dependent antibody production. This leads to suppressed cellular immunological response. The specifity of the eye immune environment is therefore important in immune and inflammatory diseases with eye involvement.(Wilbanks GA 1991).

5.4 Morphological changes in the gastrointestinal tract

In the course of reactive arthritis inflammatory bowel disease is observed. It concerns: the ileocecal valve area (22%), terminal ileum (12%) and the colon (3%). In 49% of cases abundant infiltration of inflammatory cells to the lining of the lamina propia of the mucosa is being observed along with the partial flattening of intestinal villi, hyperplasia of the cript epithelial cells, infiltration of cripts' epithelium by neutrophils and cripts abscesses. In 18% erosions of intestinal epithelium with or without granuloma are present (Cuvelier et all, 1987).

5.5 Morphological changes in the circulatory system

The presence of inflammatory changes concerning the aortic arch and ascending aorta (aortitis) often leads to aorta enlargement and aortic valve regurgitation.

6. Diagnostic criteria of reactive arthritis

The reactive arthritis belongs to the spondyloarthropathies and thus must meet the classification criteria for this group of diseases, such as Amor criteria and criteria of the European Spondyloartrhopathy Study Group (ESSG). In 1996 during the Third International Workshop on Reactive Arthritis a group of experts proposed diagnostic criteria for ReA based on the presence of asymmetric peripheral arthritis (predominantly of the lower limbs) concomitant with evident prior infection and diarrhea or urethritis preceding by 4 weeks the emergence of the arthritis. In case of the lack of history of evident infection, the diagnosis should be confirmed after the exclusion of other diseases that cause inflammation of one or a few joints (Sieper et al.1999).

There are no proper criteria for ReA recognition. ACR criteria for ReA diagnosis (1981) are defined as follows: an episode of arthritis lasting more than 1 month with concurrent urethritis and /or cervitis (84,3% of sensitivity and 98,2% specificity of diagnosis); episode of arthritis lasting more than 1 month and one of: urethritis or cervicitis, *or* bilateral conjunctivitis (85.5% of sensitivity and 96.4% of specificity); the episode of arthritis, conjunctivitis and urethritis with no time limits of the episode set (50.6% of sensitivity and 98.8% of specificity), an episode of arthritis lasting more than a month with conjunctivitis and urethritis (48.2% of sensitivity and 98.8% of specificity) [Willkens et al. 1981].

7. Diagnostic tests in reactive arthritis

There is no single diagnostic test to recognize ReA. Thus it is necessary for proper diagnosis to confirm previous infection and recognize characteristic symptoms of spondyloarthropathy such as e.g. enthesitis. It is also required to perform laboratory tests confirming the infection with one of the bacteria responsible for ReA induction.

7.1 Diagnosis of Chlamydia infection

On the basis of serological tests it has been shown that Chlamydia trachomatis is a pathogen detected in 50% of ReA patients with a history of urinary tract infections, including 12-22% of cases in which the infection was asymptomatic. Often mixed infections of Chlamydia trachomatis, Chlamydia pneumoniae and Chlamydia psittaci takes place, being found in 35% of patients with conjunctivitis (Dean et al.2008). ReA develops in 7-10% of patients infected with Chlamydia pneumoniae. Serological tests used to confirm Chlamydia trachomatis infections are often difficult to interpret, as they detect high levels of antibodies in healthy individuals and cross-react with Chlamydia pneumonia antibodies. Moreover, the diagnosis cannot be based on the presence of IgG antibodies, as they may persist for many months after the infection. Serological diagnosis should therefore be based also on the determination of IgM and IgA antibodies levels, which confirm acute or chronic infection. (Bas et al 1998)

The Chlamydia infection can also be confirmed by DNA or RNA presence in urogenital system tested with PCR or LCR (ligand chain reaction). Another diagnostic possibility is detection of Chlamydia trachomatis DNA in synovial fluid.

7.2 Diagnosis of infections of Yersinia, Salmonella, Campylobacter and Shigella

Bacteriological stool examination in Yersinia and Salmonella induced ReA is useful only in case of coexisting diarrhea, as within 4 weeks of the onset of arthritis only in 9% of patients with previous diarrhea symptoms these tests yield positive results (Fendler et al. 2000). Diagnosis of these infections is based mainly on serological tests. In Yersinia-induced ReA IgG and IgA antibodies are found in 100% of patients. In 84% of ReA patients IgA antibodies against Yersinia antigen prevail from 14 up to 16 months from the first signs of infection and the increase in their level correlates with the exacerbation of arthritis. In patients with no arthritis, these antibodies disappear after 5 months. In patients with Yersinia-induced ReA as well as in patients with no arthritis, IgG antibodies may persist for a long time after the onset of the infection, but in patients with no arthritis coexisting IgA antibodies are not present. IgM antibodies persist in the body only from 1 to 3 months after the beginning of the infection. It is recommended, therefore, to determine the level of IgG, IgM and IgA antibodies in acute Re, while only the level of IgG and IgA antibodies should be determined in chronic ReA (Granfors et al. 1980).

In Salmonella-induced ReA stool culture tests prove to be not very useful and yield positive results in only 4% of patients – both with and without persistent diarrhea. In Salmonella-induced ReA all classes of antibodies may persist for a long time - from 9 to 14 months in serum (Maki-Ikola et al. 1991). Yersinia and Salmonella can survive in the body for many months and years (being detected in the peripheral blood), stimulating the production of antibodies IgA and / or IgM. The DNA of these bacteria is very rarely detected within the joint, which confirms that the mucosa and lymph nodes constitute reservoir for these organisms. Therefore the determination of bacterial DNA presence in the synovium or synovial fluid is irrelevant to ReA (Granfors et al. 1998).

Currently a well-developed diagnostic methods for Campylobacter and Shigella infections do not exist. In the case of Campylobacter infections diagnosis can be based on bacteriological (in the presence of abdominal symptoms) or serological tests. For diagnosing infection, the presence of IgA antibodies has a greater specificity than presence of IgM antibodies (Locht & Krogfeld 2002).

7.3 Determination of the presence of HLA B27 antigen

In case of symptoms which suggest ReA – and with the exclusion of other diagnosis – the determination of the HLA-B27 antigen presence increases the likelihood of correct diagnosis from 40 to 69%. The use of the serological methods and HLA-B27 typing increases the possibility of correct diagnosis to about 80% (Sieper et al.2002).

8. Occurrence

The ability of a proper assessment of the reactive arthritis incidence is limited due to: the lack of appropriate classification and diagnostic criteria, constant mobility of young people population and poor registration of venereal diseases as well as underdiagnosis of mild course ReA. Summary of data from various developing countries shows that the incidence of the reactive arthritis in the world is 100-200 per 100 000 inhabitants. Reactive arthritis is observed post Chlamydia trachomatis in 1-4 % of cases, while post Salmonella, Yersinia and Shigella infections it is observed in 2 - 4% of cases, with incidence growing to over 20% of patients with HLA-B27 antigen present. In the case of Campylobacterjejuni reactive arthritis develops in 1 - 5% of those infected.

9. Physical examination

It is necessary to control parameters of all vital signs. The physician performing the examination should pay particular attention for the signs of joint involvement (arthritis), skin and mucosal changes, eye involvement and symptoms suggesting lung pathologies (sarcoidosis).In case of patients presenting symptoms of the increased blood pressure or results of the urinanalysis deviated from the reference values, the renal involvement has to be considered.

10. Ocular examination

A basic observation may reveal red eye symptomatic for conjunctivitis, scleritis and uveitis anterior. Performing the direct ophtalmoscopy (fundoscopy) allows the detection of hyperemia of the conjunctiva adjacent to the cornea and the detection a hypopyon of the anterior chamber (inflammation in vitreous humor) - typical signs of an acute anterior uveitis. The direct ophtalmoscopy is also a basic examination in the case of the complications of uveitis, such as glaucoma or in case of any retinal changes.

If the lens is clouded by a cataract, indirect ophtalmoscopy is a useful tool as it allows the better view of the fundus of the eye.

Slit lamp examination is very important method for the evaluation of changes in the course of uveitis. This test allows assessment of iris stroma for formation of ulcers and edema, and corneal epithelium for abrasions, edema, ulcers and foreign bodies. Slit lamp findings can reveal presence of cells (leukocyte clumps) and flare (haze) in anterior chamber (evidence of protein presence) and posterior synechiae. In intermediate and posterior uveitis slit lamp examination can detect the condensations of the vitreous inflammatory cells occuring over the pars plana and ora serrata, forming “snowballs” and neovasularisation of the retinal periphery.

Of other methods used in ocular examination, ocular coherence tomography (OCT) is used in detection of cystoid macular edema in uveitis (CMO) and fluorescein angiography is

useful in diagnosis of uveitis with macular oedema and in vasculitis. To control intraocular pressure in patient with uveitis, tonometry is used.
In cases of eye pain and suspicion of sinusitis the nasoscopy and bacteriological exam of the nasal secretions are indicated.

11. Results of laboratory tests

The laboratory test results are nonspecific for the ReA and thus not useful to confirm the diagnosis, yet necessary to monitor the course of the disease. The deviations from the norm include: normocytic anemia, moderate leukocytosis with an increase in the number of neutrophils, the increase of ESR and CRP values. In general, urine test can reveal sterile pyuria with concomitant urethritis present. Antinuclear antibodies and rheumatoid factor are not present. An examination of the synovial fluid shows changes non-specific to the ReA with inflammatory fluid characteristic for other arthritis types as well. Synovial fluid is sterile without crystal presence. Synovial biopsy is nondiagnostic and shows inflammatory changes as in other arthritis.
In some cases carrying out a differential diagnosis employing serology methods to exclude other infections - viral e.g. HIV or bacterial e.g. borrelia burgdorferi - is necessary. TPHA test is used for exclusion of syphilis, while the serum Angiotensin Converting Enzyme Assay (ACE) is used in cases of suspected sarcoidosis.

12. ECG

ECG changes occur in 5 - 14% of patients with chronic ReA and most of these changes take the form of prolonged PQ segment of I- degree AV block type.

13. X-ray examinations

Radiographic changes are seen in more than 70% of patients with chronic reactive arthritis and are characterized by the picture of swelling soft tissues (especially characteristic is so-called "sausage finger"), periosteal ossification with exostosis, erosions on the articular surfaces and periarticular osteopenia. Less frequently erosions in small joints of the feet, hands, knees and sacroiliac joints are observed. The presence of enthesitis can be demonstrated on x-ray, tough ultrasound examination can reveal a much earlier stages of the erosions. In the reactive arthritis, bone proliferation develops in many places, including the periosteum and takes a linear or feathery arrangement adhering to the cortical edge, particularly along the shaft of the metacarpal and metatarsal bones, toes, distal femoral end and the ankle. Smilar changes are seen in calcaneal, ischial and femoral trochanter tendon attachments, giving a picture of feathery ossifications. The presence of enthesitis changes may suggest reactive arthritis, but cannot determine the diagnosis, because such changes may occur in other diseases (sensitivity of 30%). Radiographic evidence of the spine in reactive arthritis is associated with disease duration and its nature. 50% of patients with chronic reactive arthritis have radiographic evidence of sacroilitis. Sacroilitis is observed more frequently in patients with Chlamydia trachomatis induced reactive arthritis (32%). Erosions are most often observed at the hip bone. In the later course of the disease pseudo-dilatation of the joint, bone proliferation, sclerosis and ankylosis are observed (Martel et al.1979, Colmegna et al. 2004).

Chest x-ray is important in suspected tuberculosis or sarcoidosis and with other cases with symptoms of respiratory tract involvement. In some cases a hight resolution CT scan chest is needed.

14. Differential diagnosis

14.1 Arthritis

The differential diagnosis of reactive arthritis should be based on the exclusion of other causes of arthritis, including other forms of spondyloarthropathies, arthritis in the course of other rheumatic diseaseas, systemic diseases, such as cancer, post-infectious arthritis e.g. in Lyme disease or in the course of viral or streptococcal infections. Changes of enthesopathy - type, which are typical of reactive arthritis, may also occur in other spondyloarthropaties and other rheumatic diseases.

14.2 Differential diagnosis in patients with ReA and eye involvement

Anterior uveitis
Idiophatic anterior uveitis Spondyloarthropaties other than ReA Sarcoidosis Juvenile idiopathioc arthritis Behcet disease Relapsing polychondritis Vasculitis (Cogan syndrome, Kawasaki disease, Wegeners' syndrome) SLE Sjogren syndrome Infections (Whipple disease, Lyme disease) Others eg. Sweets' syndrome Familal granulomatous synovitis Neonatal onset multisystem inflammatory
Posterior uveitis
Sarcoidosis Eale's disease Bridshot choirodoretinopathy Behcet disease CMV Toxoplasmosis Herpes infection Tuberculosis Histoplasmosis Syphilis

Table 3. Examples of the diseases in differentiation of uveitis (Enzenauer Sterling G.West 2002)

15. The course of the disease

The duration of reactive arthritis is considered to be chronic when it extends over 6 months (Braun et al. 2000). As many as 75% of ReA patients achieve complete remission within one year of the first symptoms and in 15% of patients the disease becomes a chronic spondyloarthropathy. The chronic ReA is induced by: Yersinia - 4%, Salmonella – 19%, Shigella – 19% and Chlamydia – 17% (Leirisalo-Repo et al. 1997, Leirisalo-Repo, 1998). Sacroiliitis is reported in 14-49% of patients, while 12% to 26% of patients with ReA develop ankylosing spondylitis (van der Linden, 2000). In patients with no negative prognostic features the course of the disease can lead to spontaneous recovery or is usually benign.

16. Prognosis

The course of the reactive arthritis depends on the type of inducing bacteria, the presence of HLA-B27 antigen, gender and recurrence of arthritis. The worst prognosis is in Chlamydia induced reactive arthritis. Recovery occurs only in 30% of cases, joint pain persists in 68% of patients, recurrent arthritis occurs in 68% of patients, changes in the sacroiliiac joints are found in 49% of patients and 26% of patients develop AS - ankylosing spondylitis (Leirisalo-repo 1998, Inman 2000). Patients with HLA-B27 antigen presence have more severe course of the disease, more frequently sacroiliac joints are involved and more frequently the disease manifests itself in other organs. Male gender, positive family history of occurrence of spondyloarthropathies (including AS) and the presence of inflammation of the hip are also negative prognostic factors. In these patients the inflammation of the spine, destructive changes in the hip and the involvement of sacroiliac joints are frequent. In the first 2 years of the disease an elevated ESR (> 30 mm after 1 h), the lack of improvement after non-steroidal anti-inflammatory drugs, inflammation of the hip, reduction in spinal mobility, the occurrence of “sausage finger” in the feet, inflammation of several joints and the onset of the disease before the age of 16 – all are considered to be negative prognostic factors (Kelley et al. 2001).
Patients with eye involvement in chronic ReA may develop ocular complications such as: secondary cataract and glaucoma, cystoid macular oedema (CMO), impairment of visulal function (to the extent of the complete blindness).

17. Treatment

17.1 Treatment of extraarticular changes

The extraarticular changes should be treated in parallel with general treatment of the disease carried out by the specialists in proper field of medicine.

17.1.1 Ocular symptoms

Aims of treatment include: pain relief and easing photophobia, elimination of inflammation, prevention of complications and preservation of proper visual function (Agrawal, 2010). Conjunctivitis in reactive arthritis should be treated with locally administered antibiotics. In Chlamydia infection the local antibiotic therapy should be simultaneous with general antibiotic therapy. It is recommended to use topical 1% azithromycyn in drops 2 - 3 times daily for 2 - 3 weeks or 0.5% erythromycin ointment 3-3 times daily for 2-3 weeks. Tetracycline and quinolones can also be used locally (Chen et al. 2010).

In anterior uveitis it is recommended to use corticosteroids locally in the form of eye drops or periocular injections or systemic administration, the latter in severe cases. Systemic Glucocorticosteroids can be used in the cases when the local treatment of uveitis is not sufficient or the diseases is recurrent and bilateral. In intermediate and posterior uveitis corticosteroids in subtenon's injection may be administered.
Drugs extending pupils (mydriatics) are recommended as well to relieve pain and prevent posterior synechiae. In the case of the eye being affected in the course of the ReA, it is sometimes necessary not only to use glucocorticosteroides and non-steroidal anti-inflammatory drugs (NSAIDs), but also immunosuppressive agents like methotrexate , cyclosporine, azathiopryne . Immunosuppessive therapy is recommended in cases resistant to corticosteroids. In complications of uveitis e.g. cataract a surgery treatment should be considered. In cases of uveitis associated glaucoma the local or systemic antiglaucoma medications are used.
In CMO the local administration of NSAIDs or corticoids in posterior subtenon's injections may be employed.
The lack of response to uveitis therapy implies that we might be dealing with the masquerade syndromes of diseases such as leukemia, lymphoma, retinoblastoma, malignant melanoma, antiphospholipid syndrome and thus these illnesses should be excluded.

17.1.2 Skin lesions

Skin lesions in the course of reactive arthritis can be treated locally with keratolytic agents (e.g. used locally with salicylates), corticosteroids or calcipotriol in the form of cream or ointment. Balanitis circinata may be treated with corticosteroids such as Hydrocortisone ointment.

17.2 Treatment of arthritis and tendon attachments

17.2.1 General recommendations for treatment of reactive arthritis

In patients with reactive arthritis the limitation of physical activity is recommended, especially walking in cases with lower limbs joints affected. It is important to use physio- and kinesitherapy, together with pharmacological treatment. The treatment of reactive arthritis should be based on reducing pain, anti-inflammatory treatment and – if possible – on the infection eradication.

17.2.2 Non-steroidal anti-inflammatory drugs

The use of NSAIDs is a basic therapy in the initial diagnostic period, while prolonged therapy with these drugs is recommended only in cases with persistent inflammation. 20-25% of patients with reactive arthritis do not feel improvement after non-steroidal anti-inflammatory drugs.

17.2.3 Glucocorticoids

The use of glucocorticoids is recommended intraarticularly only (after excluding purulent arthritis), with such administration reducing the symptoms of synovitis. Oral systemic glucocorticoid treatment may prolong the elimination of the infection, while it does not affect clinical and laboratory activity of the disease. There have been no studies so far assessing the indication for the use of steroids in high dose intravenous injections (pulses) in reactive arthritis.

17.2.4 Disease-modifying drugs

In case of ineffectiveness of NSAIDs in ReA the use of disease-modifying drugs is recommended. The most commonly used drugs in this group include sulfasalazine, methotrexate, azathioprine, cyclosporine, leflunomide.

The use of sulfasalazine in 2g/24 hours dose is very effective in reactive arthritis in case of concomitant mucositis.

Sulfasalazine presents some antibacterial activity as well (Egsmose et al. 1997), being quite effective and well tolerated (Clegg et al.1996). Comparative studies have demonstrated greater efficacy of sulfasalazine in the treatment of peripheral joint involvement in reactive arthritis than in the treatment of ReA axial involvement form (Clegg et al. 1999). Methotrexate treatment is also very effective in ReA, although there are no randomized studies to evaluate its effectiveness. It has been demonstrated however, that in patients with arthritis of the spine joints the methotrexate treatment prevents the emergence of the ossification of the spine and of the erosive lesions of peripheral joints (Ritchelin et al. 2001). Azathioprine, in dose of 1 - 2 mg / kg of body weight, is effective in the treatment of ReA with peripheral joint involvement (Calin1986).

17.2.5 Biological treatment

There are no randomized trials evaluating the efficacy and safety of biological agents of anti-TNF-alpha group in the treatment of ReA. Individual publications about etanercept and infliximab treatment in ReA point to high efficacy of these drugs (Abdelmoulaet al.2008, Gill et al. 2008, Schafranski 2009, Flagg et al.2005). The use of biological agents from the anti-TNF-alpha group is restricted to the chronic form of the disease, in which disease-modifying drugs were ineffective. Such restriction in use of agents result from the risk of extending the latent infection and Chlamydia and Yersinia, associated with the administration of these drugs.

17.2.6 Antibiotic therapy

The use of antibiotics in reactive arthritis still raises controversy. Eradication of bacteria causing reactive arthritis should improve prognosis or prevent the development of reactive arthritis. Studies have shown various effects of antibiotic use for ReA induced by genitourinary infections and different effects in Enterobacteriacae-induced ReA cases.

17.2.6.1 The use of antibiotics in Chlamydia-induced ReA

A study performed on the Greenland population, in which the high incidence of HLA-B27 antigen exists, showed that the use of antibiotics in genitourinary tract infections of patients with HLA B-27 antigen significantly reduces the number of patients who develop ReA - from 37% to 10% (Bardin, 1992). It was also shown that it is vital that the sexual partner of a person who has Chlamydia infection is treated in parallel with the patient. Another study documented the use of limecycline for 3 months in patients with acute Chlamydia-induced ReA, revealing a beneficial therapeutic effect on arthritis, with an ESR reduction and normalization of C reactive protein (CRP) levels in the group treated with antibiotic (Lauhio et al. 1991).

Good results of application of tetracycline or ciprofloxacin for a period from 4 to 12 weeks in acute Chlamydia-induced ReA were also reported (Schumacher et al. 1999). Recent in vitro studies showed high efficacy of using a combination of antibiotics (azithromycin + rifampicin) in eradicating Chlamydia infection (Dreses-Werringloer et al.2001), later

confirmed in clinical studies performed with rifampicin and doxycycline (Carter et al. 2004). The therapy with rifampicin and azithromycin has been demonstrated in experimental studies to be very effective in the eradication of chronic Chlamydia pneumoniae infection (Bin et al. 2000). Eradication of Chlamydia infections affects the further course of chronic ReA, resulting in reducing inflammatory activity and pain. In some cases such treatment leads to complete remission.

17.2.6.2 The use of antibiotics in the Enterobacteriacae induced ReA

The use of antibiotics in the Enterobacteriaceae-induced ReA raises a lot of controversy. Many studies have shown no effect of antibiotic therapy used in acute or chronic ReA on the course of the disease (Sieper et al. 1999, Toivanen 2000, Yli-Kerttula, 2000). On the other hand 4-7 year-long observations of patients with Enterobacteriacae induced ReA treated with three-months course of ciprofloxacin revealed the influence of the therapy on the distant course of ReA, particularly in patients with HLA B-27 antigen and may prevent the development of chronic ReA (Yli-Kerttula, 2003). However, this requires further research.

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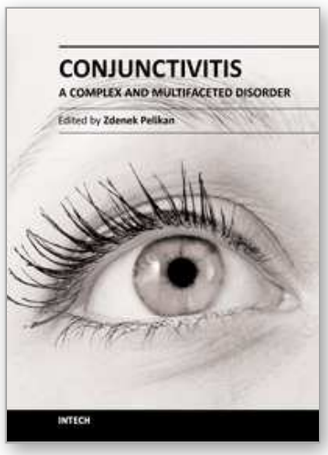

Conjunctivitis - A Complex and Multifaceted Disorder
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This book presents a number of interesting and useful aspects and facets concerning the clinical features, properties and therapeutical management of this condition. Dr. H. Mejía-López et al. present an interesting survey of the world-wide epidemiologic aspects of infectious conjunctivitis. Dr. U. Ubani evaluates conjunctival symptoms/signs participating in the clinical features of this disorder. Dr. A. Robles-Contreras et al. discuss immunologic aspects underlying possibly the conjunctivitis. Dr. Z. Pelikan presents the cytologic and concentration changes of some mediators and cytokines in the tears accompanying the secondary conjunctival response induced by the nasal challenge with allergen. Dr. S. Sahoo et al. summarize the treatment and pharmacologic control of particular clinical forms of conjunctivitis in general practice. Dr. S. Leonardi et al. explain the basic pharmacologic effects of leukotriene antagonists and their use for the treatment of allergic conjunctivitis. Dr. J.A. Capriotti et al. evaluate the therapeutical effects of various anti-adenoviral agents on the acute conjunctivitis caused by adenovirus. Dr. V. Vanzzini-Zago et al. assess the prophylactic use and efficacy of "povidone-iodium solution", prior the ocular surgery. Dr. F. Abazi et al. present the clinical features, diagnostic and therapeutical aspects of "neonatal conjunctivitis". Dr. I.A. Chaudhry et al. review the special sub-form of conjunctivitis, being a part of the "Trachoma". Dr. B. Kwiatkowska and Dr. M. Maślińska describe the clinical, pathophysiologic and immunologic features of conjunctivitis. Dr. S. Naem reviews the conjunctivitis form caused by Thelazia nematodes, occurring principally in animals.

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