REACTIVE ARTHRITIS IN CHILDREN

Kholmuradova Zilola Ergashevna

Assistant, Department of Pediatrics, Faculty of Medicine.

Samarkand. Uzbekistan.

Annotation: *Inflammatory joint diseases are one of the pressing problems of modern pediatric rheumatology. Among them, for many years, the leading role belonged to juvenile rheumatoid arthritis (JRA). However, in recent years there has been a tendency towards an increase in reactive arthritis (ReA) in children. The frequency of ReA in the structure of rheumatic diseases in various countries of the world ranges from 8 to 41% [1].*

Key words: *reactive arthritis, treatment, children.*

The data presented indicate the importance of ReA in childhood and dictate the need for a differentiated diagnostic and therapeutic approach to various variants of this joint pathology in children.

Reactive arthritis is an aseptic (non-purulent) joint disease that develops in response to an extra-articular infection in which the causative agent cannot be isolated from the joint.

The term “reactive arthritis” was proposed by Finnish researchers Ahvonen et al., who were the first to describe arthritis that developed after yersinia infection. Subsequently, “reactive arthritis” completely replaced the one proposed by A.I. Nesterov’s term “infectious-allergic arthritis”. Previously, it was believed that ReA was “sterile”, since neither the living causative agent nor its antigens could be isolated from the joint cavity. Subsequently, as methodological techniques improved, individual microbial antigens and even microorganisms capable of reproduction were isolated from joint tissues and synovial fluid [2]. During our long-term observations of children with ReA, we were repeatedly able to isolate chlamydial DNA from the synovial fluid, and in one case, E. coli. In this regard, there are indications in the literature that the term “reactive arthritis”

should be used with caution [2,3,4]. However, it is still widespread both in the literature and in international classifications of rheumatic diseases. In the working classification of rheumatic diseases, three groups of ReA were distinguished:

- post entero colitic
- urogenital
- after a nasopharyngeal infection

At the IV International Workshop on Reactive Arthritis (Berlin), agreement was reached on the definition of reactive arthritis. It is recommended to call inflammatory (non-purulent) joint diseases that develop shortly (usually no later than 4 weeks) after an acute intestinal or urogenital infection as reactive arthritis. The etiological factors of post-enterocolitic ReA should be considered Yersinia, Salmonella, Shigella, Helicobacter; urogenic - chlamydia, ureaplasma. Other forms of arthritis - post-streptococcal, post-viral, Lyme arthritis, according to the conclusion of the experts of the International Meeting, should be combined with the term “arthritis associated with infection”, and this group should not include septic, purulent arthritis. However, a number of issues require further study. In particular, the list of microbial agents that initiate ReA remains incomplete. Possibly, mycoplasma, clostridia and other infectious agents have a trigger effect [4].

Based on the above, it follows that the infectious agent is the leading one in the development of ReA. The immune response is manifested by the production of antibodies circulating in the blood and synovial fluid. A long-lasting elevated level of antibodies indicates the presence of an infectious agent, on the one hand, and the persistence of microbial antigens in tissues and synovial fluid, on the other. In addition, numerous literature data indicate the importance of genetic predisposition [2,4,5,6,7]. The authors note a close relationship between ReA and one of the antigens of the major histocompatibility complex – HLA-B27. Moreover, the association of HLA-B27 with urogenic arthritis is observed in 80-90% of cases, with postenterocolitic arthritis - in 56%. At the same time, the role of HLA-B27 in the development of ReA has not been fully studied. There are only a few hypotheses:

– HLA-B27, being a receptor for microbes, promotes their spread in the body, including in the joint cavity;

– HLA-B27, participating in cellular immune reactions, is able to present microbial cells to cytotoxic T lymphocytes. In this case, an inadequate immune response and persistence of the microbe are possible.
– In recent years, there have been many supporters of the theory of microbial mimicry, when there are similar proteins (antigenic determinants) in a microbe and HLA-B27. In this case, the immune response is directed both against the infectious agent and the tissue's own cells, having a damaging effect on them. Cross-reacting antibodies weaken the immune response against the infectious agent, which prevents complete elimination and contributes to its persistence [1,8].

A common clinical feature of ReA is a previous infection. By the time arthritis develops, clinical signs of infection usually subside. A mild, asymptomatic course of urogenital infections is possible. In some cases, arthritis develops simultaneously with diarrhea, urinary tract infection, and eye damage (conjunctivitis, iritis, iridocyclitis). At the onset of articular syndrome, low-grade fever, weakness, and loss of appetite are often noted.

Clinical features of ReA include:

• acute nature of the articular syndrome

• asymmetry of the articular syndrome

• oligo- or monoarthritis of medium and large joints of the lower extremities

• possibility of torpid course of articular syndrome . Postenterocolitic ReA is characterized by an acute onset with a typical localization - in the joints of the lower extremities. However, sometimes the wrist joints may be involved in the process. In this case, general reactions are expressed in the form of fever (38.0-39.0C), leukocytosis, acceleration of ESR to 40-45 mm/hour. For this variant of ReA, a torpid course of the articular syndrome is typical, averaging 3-5 months. In some cases, transformation into JRA is possible. Urogenic ReA is characterized by a torpid course combined with high laboratory activity.

One of the variants of ReA is Reiter's syndrome (according to ICD-10 M02.3 - Reiter's disease). The disease develops in temporary connection with intestinal or urogenital infections. Currently, Reiter's syndrome is considered to be a consequence of chlamydial infection. At the same time, Chlamydia pneumoniae is detected in 90% of children, and Chlamydia trachomatis is detected in only 10% [10].

The clinical picture is characterized by the presence of urethro-oculo-synovial syndrome. In children, damage to the urogenital tract is manifested by leukocyturia, dysuria, symptoms of vulvitis or vulvovaginitis in girls, balanitis or balanoposthitis in boys. Eye damage in the form of conjunctivitis is short-lived and ephemeral, but it may recur. Literary data indicate the possibility of developing iridocyclitis and uveitis [3,5,9].

Articular syndrome in the form of acute asymmetric arthritis occurs with the accumulation of a large amount of synovial fluid (up to 50-70 ml in the knee joints), involving large and small joints of the lower extremities. Damage to the first toe with the formation of a “sausage-shaped” deformity is quite common. The “staircase symptom” is characteristic, in which there is a gradual involvement of the joints from bottom to top. Periarticular lesions in the form of bursitis, tendovaginitis, enthesitis and enthesopathies are typical. The classic triad of symptoms may be joined by skin lesions in the form of keratoderma of the palms and feet, psoriasis-like plaques on the skin of the face, trunk, and limbs. With a prolonged course, onychodystrophy develops (change in nail color, fragility, roughness, tuberosity), which is often regarded as a mycotic lesion. The duration of Reiter's syndrome in an acute course is 2-3 months; in a prolonged course, transformation into JRA is possible.

Reactive arthritis is classified as a seronegative spondyloarthropathy. This is explained by the identical clinical symptoms of ReA and the onset of spondyloarthropathy. The latter manifest in childhood and adolescence with reactive asymmetric oligoarthritis of the lower extremities, which is combined with enthesitis. Damage to the hip joints deserves special attention. In 1/3 of children and adolescents, arthritis of the hip joints is the first symptom of

spondyloarthropathy. At the onset, other joints are affected only in 10-15% of patients [4,5]. Damage to the sacroiliac joints significantly increases the likelihood of spondyloarthropathies.

The onset of spondyloarthropathy in children with clinical signs of ReA can be suspected by specific clinical signs that have occurred in the past or are detected at the time of observation. These include:

• pain in the gluteal muscles (constant or intermittent);

• pain in the sacrum or morning stiffness in the lumbar region;

• pain in the heel, sole or other enthesopathy;

• the presence of a "sausage-shaped" finger on a hand or foot;

• diarrhea, dysuria a month before the onset of arthritis. Timely specific nosological diagnosis of spondyloarthropathy in children is possible only through dynamic observation, laboratory and radiation diagnostics.

Examination of children with ReA includes:

1. Family history with an emphasis on diseases of the musculoskeletal system, metabolic disorders.

2. Epidemiological history.

3. Clinical blood test.

4. General urine analysis.

5. Biochemical blood test (CRP, protein fractions, fibrinogen, uric acid, kidney and liver function indicators).

6. To identify the infectious agent:

– microbiological examination of feces, synovial fluid, scrapings from the conjunctiva, external genitalia;

– immunological methods to detect antibodies to antigens of enterobacteria and intracellular pathogens in synovial fluid and blood serum;

– study in urine, in the epithelium of the urogenital tract, synovial fluid of DNA and RNA of chlamydia, ureaplasma using polymerase chain reaction;
– seeding of synovial fluid, genital secretions onto cellular structures (the cultural method is the "gold standard" for clarifying the trigger role of chlamydia in joint pathology).

7. X-ray examination of joints, spine, sacroiliac joints (according to indications).

8. Electrocardiography (according to indications).

When carrying out a differential diagnosis, the following are excluded:

– acute rheumatic fever;

– infectious arthritis (septic);

– other diseases from the category of spondyloarthropathy (juvenile spondyloarthritis, onset of ankylosing spondylitis, etc.);

– seronegative JRA;

– metabolic arthritis;

– synovitis against the background of joint hypermobility syndrome;

– other inflammatory diseases of the joints.

The goal of treatment for ReA in children is to eliminate the causative factor - the infectious agent, as well as cure or achieve stable clinical and laboratory remission of the articular syndrome.

All children with ReA receive drug therapy taking into account age, individual effectiveness, the appropriate trigger agent, as well as the severity and nature of the articular syndrome.

1. Antibacterial therapy is prescribed when an infection is detected. This applies primarily to chlamydial, myco- and uroplasma infections, as well as Helicobacter pylori. The drugs of choice are new generation macrolides that accumulate intracellularly in inflamed tissues.

It should be noted that with increasing duration of one course of antibacterial therapy, the effectiveness of treatment does not increase [6]. If articular syndrome persists, a second course of antibiotics may be prescribed. In this case, the interval between the first and second courses should be at least 5-7 days. It must be remembered that penicillin drugs are not indicated for chlamydial infection due to their transformation into L-forms, which are insensitive to antibiotics. In addition, immunocompetent cells (phagocytes, T cells) practically do not react to L-forms, which contributes to the persistence of the pathogen and the chronicity of the articular syndrome. According to our observations, a

combination of antibacterial therapy with one of the immunocorrective drugs - lycopid, which stimulates the functional activity of phagocytes and increases the synthesis of specific antibodies, is justified. For children aged 1.5 to 15 years, licopid was prescribed at a dose of 1 mg/day. The duration of the course was no more than 15 days. The start of therapy with licopid preceded the prescription of a macrolide (5 days - licopid, then 10 days - macrolide + licopid). In the case of chronic articular syndrome, immunocorrective therapy requires great caution, since the development of an immunoaggressive stage of the inflammatory process cannot be excluded.

In postenterocolitic ReA, antibacterial therapy is usually ineffective [7].

2. Non-steroidal anti-inflammatory drugs (NSAIDs). This class of pharmacological agents is a necessary component of the treatment of ReA. NSAIDs quickly reduce pain and reduce the intensity of the inflammatory process by suppressing the activity of the enzyme cyclooxygenase (COX), which is involved in the synthesis of prostaglandins. In the last decade, the understanding of the points of application of NSAIDs in the regulation of prostaglandin synthesis has expanded significantly. Two isoforms of COX have been discovered: COX-1 and COX-2, which play different roles in this regulation. It is COX-2 that takes part in the synthesis of pro-inflammatory prostaglandins, which enhance the processes of inflammation and cell proliferation. The activity of COX-1 determines the production of prostaglandins, which are responsible for normal physiological cellular reactions not associated with inflammation [8]. NSAIDs, acting on both isoforms of COX, reduce the activity of the inflammatory process and at the same time can lead to undesirable reactions from various organs and systems. Currently, NSAIDs that can selectively inhibit COX-2 (meloxicam, nimesulide) have been developed and are widely used.

From the data in this table it follows that NSAID therapy has age restrictions. The drugs of choice for children under 5 years of age are paracetamol and ibuprofen. However, the minimum effective therapeutic dose of ibuprofen is lower than paracetamol, which significantly reduces the risk of possible adverse reactions. Ibuprofen blocks COX both in the central nervous system and at the

site of inflammation, which causes a distinct anti-inflammatory effect. The analgesic effect of the drug is also double (central and peripheral), and therefore it is more pronounced than that of paracetamol [5]. The drug does not form toxic metabolites, is well tolerated and can even be prescribed to infants. 3. Local therapy for ReA includes intra-articular administration of glucocorticosteroids (GC) and local use of NSAIDs in the form of ointments, creams, and gels. Intra-articular administration of HA has a distinct anti-inflammatory and analgesic effect. In combination with the above therapy, as a rule, 1-3 injections are sufficient to relieve articular syndrome.

The use of ointment forms of NSAIDs, especially in children of the first years of life, is safer and allows you to reduce the dose of orally taken drugs. Gels are preferred, since the alcohol solution present in their composition contributes to the fastest transcutaneous effect. In this case, NSAIDs suppress the production of inflammatory mediators directly in the tissues surrounding the joint. 4. If ReA is torpid or the process is chronic, sulfasalazine is indicated in a daily dose of 20-30 mg/kg, but not more than 1.5-2 g per day. The initial dose is 125-250 mg per day, the dose is increased to the calculated dose gradually, once every 5-7 days. The clinical effect occurs after 5-6 weeks of treatment. The duration of the course is individual, but not less than 2 months. Thus, when carrying out complex therapy for ReA in children, one should take into account the biological characteristics of the infectious agent, evaluate the nature of its interaction with the macroorganism, and synchronize treatment with the activity and nature of the course, severity, and dynamics of the inflammatory process in the joints.

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