Post-Streptococcal Uveitis

Konovalova N.V., Dr. Sc. (Med.); **Savko V.V.,** Dr. Sc. (Med.); **Khramenko N.I.,** Cand. Sc. (Med.); **Guzun O.V.,** Cand. Sc. (Med.); **Slobodianyk S.B.,** Cand. Sc. (Med.); **Zhuravok Iu.A.,** Cand. Sc. (Med.); **Savko V.V., Jr.,** Cand. Sc. (Med.)

SI "Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine"; *Odesa Ukraine)*

Post-streptococcal uveitis refers to the most severe inflammatory conditions of the eye. It often affects young people leading to incapacity for work and physical disability. The clinical features, diagnosis, and treatment of uveitis after a streptococcal infection are described in the paper.

Keywords:
uveitis, streptococcus, diagnosis, treatment

Introduction

Uveitis is one of the most severe inflammatory diseases of the eye which often affects young people of the working-age. Uveitis is characterized by high rates of complication occurrence which leads to vision impairment and blindness of an affected eye with a fellow eye often involved in the process. This defines the social significance of the disease [1, 2, 3]. Uveitis can be infectious and non-infectious. In the etiology of uveitis, the prevalence of systemic pathology of the body (ankylosing spondylitis, rheumatoid arthritis, Behçet's disease) is 40-50% [1, 3, 5, 6]. This group of uveitis is characterized by a distinct inclination to spreading and recurrence of intraocular inflammation and developing complications which, in the absence of timely and effective treatment, can lead to irreversible vision loss [7, 11]. In pathogenesis of non-infectious uveitis, the leading role belongs to autoimmune mechanisms, involving a great number of factors: eye tissue antigens, toxins and non-specific agents, heterogenic antigens, free radicals, nitrogen oxide, pro-inflammatory cytokines (tumour necrosis factor, interleukins), chemokines, adhesion molecules, T- and B-lymphocytes [2, 3, 4].

Rheumatism is a systemic inflammatory disease of connective tissue which develops due to streptococcal infection in genetically predisposed persons with cardiac and vascular disease. Rheumatic disorders are characterized by clinical polymorphism. The primary role in the development of rheumatism belongs to streptococcal infection (Group A beta-hemolytic streptococcus) although immune disorders are also of substantial significance. The pathologic process in rheumatism is determined by two major factors: a toxic effect of streptococcus-produced cardiotoxic enzymes and the presence of common antigenic determinants in some streptococcus strains and cardiac and choroid tissues. Uveitis is accompanied by rheumatoid arthritis (RA) in 15-20% of cases. In seronegative arthritis, retinal vasculitis develops in 24.1% of cases [13, 19]. Apart from uveitis, conjunctivitis, scleritis, keratitis, glaucoma, and cataract are also revealed in such patients [10, 11, 19]. Scleritis is diagnosed in 5-10% of RA patients [20].

Various exogenic, endogenous (type 2 collagen, stress proteins) and non-specific factors can play a specific part in the etiology of the rheumatoid process. There are data on the association of rheumatoid arthritis with carrying HLA class II alleles. It is supposed that autoimmune mechanisms are involved in the pathogenesis of true rheumatic lesion, which is evidenced by the cross-reactivity between streptococcus antigens and cardiac and ocular tissues as well as the presence of cross-reacting antibodies to the toxic action of some streptococcus enzymes in patients. Tissue alterations are based on the systemic disorganization of connective tissue in combination with specific proliferative and non-specific exudative proliferative reactions in tissues around small vessels with affected microcirculatory vessels [11, 12]. Clinically, rheumatoid disease affects the heart

(carditis), joints (polyarthritis), brain (Sydenham's chorea, encephalopathy, meningoencephalitis), eyes (myositis, episcleritis, keratitis, uveitis, secondary glaucoma, retinal vasculitis, neuritis), skin (erythema annulare centrifugum, rheumatoid nodules, pleuritis, abdominal syndrome) [9, 19].

The clinical picture of rheumatism is highly variable. There are several periods in the rheumatoid development of the process: the first latent period includes the interval between recovery from tonsillitis, acute respiratory disease, or other acute infection and early symptoms of rheumatism. It lasts from 2 to 4 weeks and can run asymptomatically or as prolonged convalescence.

The second period is acute rheumatic fever. The third period is manifested by multivarious forms of reversible rheumatism.

The course of the disease is more often protracted and continuously recurrent, which leads to progressive circulatory failure and other complications determining the poor clinical outcome of rheumatism [1, 10, 13, 17, 18].

Ocular symptoms. Patients with rheumatism can suffer from tendonitis, myitis, episcleritis, scleritis, sclerosing keratitis, uveitis, retinal vasculitis as ocular complications of the rheumatic process. [5, 6, 10, 19].

Uveitis occurs in 3-8% of patients with rheumatism. Uveitis can be categorized according to the localization as anterior (iritis, iridocyclitis), intermediate (posterior cyclitis, peripheral uveitis), posterior (retinal vasculitis, choroiditis, chorioretinitis), or total (panuveitis). In some cases, an ocular lesion in rheumatic disease takes the form of retinal vasculitis and papillitis with the optic nerve involved in the process. Iridocyclitis in rheumatic disease has an acute onset and a stormy course of the disease in adults and a slow areactive disease course in children. Both eyes, either simultaneously or in sequence, can be affected. The process is diffuse and non-granulomatous. In children, iridocyclitis starts unnoticed and develops with a vague clinical picture and the absence of pericorneal hyperemia. In adolescence, iridocyclitis has an acute onset and symptoms of eye irritation, often followed by retinal vasculitis leading to vision loss [1, 6].

What stands out i n the clinical picture is the presence of pronounced pericorneal hyperemia. On the background of the edematous corneal endothelium, biomicroscopy reveals small and bigger precipitates, conglomeration of semi-transparant exudates in the anterior chamber, and a shaded stromal pattern of the iris. The iris is soft and edematous, with single posterior synechiae, small granulomas on the extreme periphery of the iris, and a narrow pupil. In the vitreous there can be seen destruction with a suspension of disordered fibers and exudative flakes, fine-grit destruction of the anterior segment in a form a polymorphous suspension [6, 7, 8, 9, 10, 11, 20].

In panuveitis, more severe semifixed bonds and films can be revealed in the posterior segment of the eye against the pathologically altered vitreous. In retinal vasculitis, destructive and proliferative processes develop in vessel walls of arterioles and arteries; these processes can be detected ophthalmoscopically as several widened retinal arteries and veins with the presence of greyish cuffs or sheaths around second and third-order vessels; cuffing or sheathing can involve several vessels or “linings”, resembling frosted branch, located on one side of a vessel. In addition, there can be sheaths and exudates in a form of round/oval greyish clots (pink-and-yellow foci can be formed in the macular area and in the periphery of the fundus). The optic nerve, being involved in the process, has the blurred contour, hyperemia of the optic disc, and neuritis symptoms [8, 9, 10, 11, 12, 14].

Rheumatism can also cause acute vascular disorders in vessels of the retina and optic nerve. Common vascular damage involves the optic nerve vessels; herewith, reactive papillitis is observed on the fundus. In addition, on the optic nerve appear exudates which cover the vascular tunnel and most of the optic disc surface. In the presence of macular edema, visual acuity is decreased [8, 11].

One of the rare complications of rheumatism is sclerosing keratitis and, in more severe cases, progressing scleritis, keratitis, and perforating scleromalacia, resulting in eyeball atrophy and sub-atrophy. There also can be acute and sub-acute rheumatic tendonitis and myositis of one or all extraocular muscles [1, 10, 12, 20].

Diagnosis of the rheumatoid disease includes determination of antistreptococcal antibody titers (antistreptolysin O) in the blood serum, which confirms past infectious disease of streptococcal etiology; determination of erythrocyte sedimentation rate (ESR), C-reactive protein, and sialic acid level, which allows assessing the intensity of inflammation. Peripheral blood studies include counts of thrombocytes, erythrocytes, hemoglobin, leukocytes, leukocytes with differential, and ESR. With acute disease onset, neutrophilia and decreased ESR are noted as early as first days and often remains for a long time after clinical signs disappear. Antistreptococcal antibody rate in a titer with a ratio more than 1:250 is observed in 2/3 of patients. Bacteriological tests of throat swab samples show group A beta-hemolytic streptococcus. In single culturing, streptococcus is revealed in 20-45% of cases, serial culturing is more informative for streptococcus detection [6, 13].

Biochemical studies include measurements of total protein, protein fractions, urea, creatinine, bilirubin, potassium, sodium, ionized calcium, transaminase, and alkaline phosphatase. Immunological studies include measurements of immunoglobulins A, M, G, C-reactive protein, rheumatoid factor, the presence of antinuclear factor (ANF).

Human Leukocyte Antigen (HLA)-B27 is a specific protein located on the surface of immune cells and which carrier state is associated with a high risk of seronegative spondyloarthritis. HLA-B27 is revealed in 90-95% of patients with ankylosing spondylitis, in 75% of those with Reiter's syndrome, in 80-90% of those with juvenile

ankylosing spondylitis arthritis, and in 60-90% of patients with enteropathic arthritis. The incidence of HLA-B27 in patients with the joint disease (gout, septic arthritis) is not higher than 7-8%. In this regard, detection of HLA-B27 is of great diagnostic value in the clinical practice of rheumatoid diseases [9, 18, 19].

In addition, electrocardiography, ultrasound examination of the abdomen, heart, and kidney, roentgenography of the chest, arthritic joints, and, if necessary, spine, sacroiliac joints, can be performed.

Echocardiography is reasonable for detecting heart defects and pericarditis. Echocardiography is crucial in specifying the character of heart rhythm disorders. Rheumatoid diseases are associated with immune system disorders. At one point, the body starts producing antibodies which are toxic to self-proteins, thus, inducing a chronic inflammatory process. A critical role in pathogenesis of these conditions play immune disorders as a shortage of T suppressor cells, a predominance of T helper cells, and increased activity of B- lymphocytes. Interaction of bacteria with the immune system can lead to development of several outcome variants: stimulation of protective immunity; immune suppression; unfavorable immune reactions which can cause damage to host tissues.

BETA-hemolytic streptococcus, especially of group A, most commonly causes localized infection of upper air passages, skin, and eyes. Damage to tissues can be caused by various products of streptococcus. They include specific toxins (streptolysin and streptococcal pyrogenic exotoxin), which lyse tissues; cycling cells, including leucocytes, specific enzymes (hyaluronidase and streptokinase), which contribute to spreading of infection; and superficial components of a streptococcal cell wall. All these proteins are immunogenic and M-protein is a major virulence factor. Local inflammation leads to leukocytosis in peripheral blood, followed by leucocytic infiltration in the inflammation site, and to local purulence. Specific antibodies appear not until the fourth day and are believed not to play an important role in localizing acute primary streptococcus infection. An important component of inflammation is autoallergy. The ability of lymphocytes and macrophages to identify antigenic determinants of self cells (autoantigen) is considered not as pathology but a necessary condition for immune system functioning. Formation of autobodies, antigen/autobody complexes is also a physiologic mechanism necessary for clearance of potentially pathogenic substances and cell destruction products. In some cases, autoallergic and immune complex processes have a pathologic character; in certain conditions, normal tissue components are damaged in structure and functions and altered self-tissues act as non-self-antigens and, subsequent, produce autoantibodies to damaged tissues [7, 8, 12, 13, 15, 17, 19, 20]. The autoallergic condition can develop in uveitis due to the fact that ocular tissues carry expressed organ specificity. Proteins in the anterior uveal tract are specific and differ from those in the posterior segment. At the same time, the ciliary body, iris, and choroid have antigens which are similar to each other to those in the retina, optic nerve, brain tissues, and renal vessels [3]. The quote data make it possible, to a certain degree, to explain the possibility of developing not only isolated iridocyclitis but panuveitis in systemic diseases (rheumatic disease, Reiter's syndrome). In experiment, autoallergic chorioretinitis and panuveitis were simulated using S-antigen, a soluble antigen of outer retinal segments [2, 8].

Treatment of severe non-infectious uveitis is a challenging task. In systemic autoimmune disease, immunosuppressive therapy influences simultaneously both the choroid of the eye and systemic manifestations of the disease. Systemic treatment in uveitis is applied regardless of the presence or absence of systemic manifestations [6, 9, 15]. Glucocorticosteroids are generally accepted as first-line drugs. However, their use, even in high dose, not always results in relief of inflammation, which is determined by resistance to treatment, severe adverse effects, acute uveitis condition if corticosteroids dose is reduced, and late treatment. If steroid therapy is insufficient with side effects and the course of uveitis is complicated and has a risk of vision loss, immune suppressive therapy is prescribed. However, approximately 40% of non-infectious uveitis and retinal vasculitis refer to idiopathic inflammations of the eye where comprehensive examinations of a patient do not reveal any systemic disease. There are data on increased therapeutic efficacy and decreased rates of side effects when a combination of a low dose of methotrexate and prednisolone is used [14, 15]. In low doses (from 5 to 25 mg a week), methotrexate has an anti-inflammatory rather than anti-proliferative effect, which is associated with a release of anti-inflammatory cytokines. Besides, cyclosporine A has been found to be efficacious. Cyclosporine A in low dose (up to 5.0 mg per kg, per day) does not cause severe side effects [3].

Retinal vasculitis is a characteristic of rheumatoid involvement in the retina and requires neuroprotection. Ischemic damage results in cell loss, including loss of axons, myelin sheaths, and glial cells. A risk factor of neuroretinitis is hypoperfusion in the posterior ciliary arteries. In peripheral vascular disease of the retina and optic nerve, prostaglandins and their analogs are most effective in reducing pressure [3, 4, 12].

Drug treatment for rheumatic diseases has developed medications from monoclonal antibodies to tumour necrosis factor-alpha to small molecule inhibitors. Pathogenesis of rheumatoid arthritis has been decoded with discovering a great number of new molecules and signal pathway participating in pathogenesis of the disease, which has made it possible to produce drugs, immune activation agents, affecting major clinical symptoms of rheumatoid manifestations and progression mechanisms, and enabling remission which is the main purpose of treatment. New biological drugs are characterized to have an effect on B-cells as well as on stimulation of T-cells. There is a new

group of biological agents among which are infliximab, rituximab, abatacept, tocilizumab, and certolizumab pegol [17].

Thus, a combination of antibacterial, biological, immune suppressive and hormonal drugs makes it possible to manage the inflammation process earlier. Direct and indirect neuroprotection contributes to improvement of biochemical and regenerative properties of nerve cells, contributes to stimulation of ion-exchange pumps and receptors, has an anti-edematous action, and inhibits apoptosis.

To conclude, first, for pathogenetically substantiated treatment, it is required to perform comprehensive complex examination including both morphometric and functional tests.

Second, rational use of antibacterial, biological, immune suppressive and hormonal drugs makes it possible to manage the inflammation process earlier.

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