Acute rheumatic fever (rheumatism)

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Acute rheumatic fever (ARF, rheumatism, disease of Sokol’skiy-Bouillaud) -

infection provoked by rheumatic strains of β-hemolytic streptococcus of group A, manifesting as systemic inflammatory disease of connective tissue with predominant affection of heart (rheumocarditis), joints (rheumatic polyarthritis), brain (rheumatic chorea), and skin (annular erythema, rheumatic nodules)
Actuality of the theme

- ARF develops more frequently in children (from 4-5 up to 15-18 years) and young persons

- In 20-25% persons suffering from primary rheumocarditis acquired heart disease is formed, that essentially influences quality of life, leads to disability, development of chronic cardiac insufficiency or even death. Such patients are in need of cardiosurgical intervention – correction of acquired heart disease.
Actuality of the theme

- Nowadays approximately 15.6 mln of people around the world suffer from ARF, almost 2.4 mln among them – children aged from 5 up to 14 years.
- More than 500 000 cases are newly registered annually.
- More than 350 000 persons die due to consequences of ARF.
- More than 4 000 kids suffer from chronic rheumatic heart diseases.
- Morbidity with ARF among children in industrially developed countries is 1-5/100 000 per year (0.001-0.005%), in developing countries – is 100 times greater.
Actuality of the theme

- Sickness rate of ARF among children of 0-17 years old in Ukraine was 0.03/1000 in 2008 and 1009y.y. (268 and 213 children correspondently)
- Most high indices were present in Cherkasskaya region (0.19/1000, 43 children) and Kharkovskaya region (0.1/1000, 42 children)
- Prevalence of ARF in Ukraine among children from 0 up to 17 years was 0.07 (612 children) in 2008y., and 0.06 (459 children) in 2009y.
- Upon data of Ministry of Public Health of Ukraine sickness rate of chronic rheumatic cardiac disease (CRCD) among children from 0 up to 17 years was 0.04 (359 children) in 2008y., and 0.03 (257 children) in 2009y.
- Prevalence of CRCD was 0.59 (4876 children) in 2008y., and 0.49 (4003 children) in 2009y.
Etiology

- Development of ARF is connected with streptococcal infection. So called “rheumatic” strains of β-hemolytic streptococcus of group A (M1, M3, M5, M6, M14, M18, M19, M24, M27, M29) are associated with ARF most frequently.

- Chronologic connection of the disease with streptococcal infections of nasopharynx (tonsillitis, pharyngitis) indirectly testifies to role of streptococcal infection. Time interval exists when symptoms of systemic inflammatory disease of connective tissue typical for ARF appear in 2-3 weeks after past acute streptococcal nasopharyngeal infection.
Modern theory of ARF pathogenesis –
toxic-immunologic

1. Affection of tissues, including tissues of heart, is
   stipulated by direct toxic action of specific
   streptococcal products (toxins) among which:

2. M-protein, which depresses phagocytosis, and is
   an antigen cross reacting with cardiac membranes

3. Streptolysines O and S, streptokynase,
   hyaluronidase, proteininases, DNA-ase B –
   enzymes of streptococcus which are able directly
   provoke tissue’s affections, and indirectly as well,
   promoting kinin system that favors depolymerization of hyaluronic acid.
2. Production of antitoxic antibodies: antistreptolysin O (ASLO), antistreptokinase (ASK), antistreptohyaluronidase (ASH), antidesoxyribonuclease B (antiDNA-ase B) and immune complexes.

2.1. High titer of these factors in blood affects microcirculatory bloodstream with development of destructive-productive vasculitis.
2.2. Antistreptococcal antibodies \textbf{cross react with human tissues} due to phenomenon of \textbf{“antigenic mimicry”} (there is similarity between epitops of microbial cell and structures of macroorganism – sarcolemmas of cardiomyocytes, cardiac myosin, cardiac connective tissue, glycoprotein of cardiac valves, vessels wall, cytoplasma of neurons of subthalamic and caudate nucleus of the brain, epithelium of cortex and medullar zones of thymus). \textbf{Affection} of macroorganism’s structures with development of typical clinical symptoms of the disease takes place.
2.3. Humoral and cellular immunologic disorders in ARF are characterized by increase of titers of ASLO, ASH, ASK, dysimmunoglobulinemia, increase of absolute quantity of B-lymphocytes and decrease of percent and absolute quantity of T-lymphocytes.

3. Function of tissue basophils suffers a lot, their degranulation is increased, biologically active substances (mediators of inflammation – histamine, serotonin, bradykinines etc.) pass to tissues and blood stream that favors development of inflammation.
Morphologic stages of ARF

There are 4 morphologic stages of connective tissue’s affection in ARF:

- **Stage of mucoid degeneration** – it’s reversible stage (phase) of the disease with duration of 1.5-2 mo. Depolymerization of connective tissue’s main substance with accumulation of acid mucopolysaccharides takes place.

- **Stage of fibrinoid changes** – fibrinoid necrosis (irreversible phase). It’s characterized by disorganization of collagen fibers, their degeneration, disintegration of collagen and accumulation of fibrinoid.
Morphologic stages of ARF

- **Proliferative stage** – stage of granulomatosis: specific granulomas (granulomas of Ashoff-Talalaev) are formed around foci of pathologic necrosis, predominantly perivascular, in parietal endocardium, near valves. They consist of big basophilic histiocytes, lymphocytes, mast and plasmatic cells. Natural rheumatic granuloma is formed only in the heart.

- **Stage of sclerosis**: granuloma’s cells are transformed into fibroblasts and scar tissue is developed on the place of granuloma. Rheumatic process passes above mentioned cycles during 6 months.
Changes of vessels of microcirculatory bloodstream which are found in all organs are important non-specific factors of ARF for pathogenesis and morphogenesis.

Mucous membranes are involved gradually into the process, especially in high activity of ARF, stipulating a picture of serous, serous-fibrinous inflammation.

Manifestations of connective tissue’s disorganization, exudative inflammation, and vasculitis are present in articular tissues in clinically marked polyarthritis. Reversibility of the process not only at the stage of mucoid degeneration, but at the initial stages of fibrinoid changes also, is the peculiarity of rheumatic affection in childhood.
Involvement of brain vessels into rheumatic process underlies affection of nervous system. Change of the cells of striate body, subthalamic nuclei, brain cortex and medulla is pathologic substrate of rheumatic chorea.

Affection of skin and subcutaneous fat manifests with vasculitis, endothelitis and focal inflammatory infiltration (T. Benza, 2004)
Peculiarities of clinical manifestations of ARF in childhood

*Rheumatic polyarthritis* (RP) is registered frequently.

Main signs: acute onset, fever, pain in joints, intumescence (due to sinovitis and affection of periarticular tissues), limitation of movements; increase of temperature and redness of tissues above joints is possible.
Differential characteristics of RP:
- involvement of big and medium joints in pathologic process, more often knee, talocrural, radiocarpal and elbow;
- dissociation between scanty clinical data and intensity of subjective symptomatology — excruciating pains in affected joints, especially at movements;
- symmetry of affection;
- migratory character;
- absence of deformations;
- quick regression of the process (on the background of anti-inflammatory therapy pains disappear during several days and even hours)
- in 10-15% of patients polyarthralgias are present.

At steady symmetric arthritis of big joints, insufficient answer for NSAID therapy and absence of clinico-instrumental signs of carditis it’s necessary to think about post-streptococcal reactive arthritis.
BUT! They say: «Rheumatism licks the joints and bites the heart».  

*Rheumatic carditis* – main symptom of ARF (90-95% of cases), which determines severity of the course and its outcome (in 30-70% patients with the first attack and in 73-90% patients with repeated attack).

- **Endocardium and myocardium** are affected most frequently (endomyocarditis), sometimes in association with pericarditis (pancarditis).

- **Severity of carditis’ course** is determined by
  - increase of heart’s size,
  - weakening of the 1-st tone at the apex (up to muffle, so called “cotton” tone),
  - disorder of cardiac rhythm (tachycardia, tachyarrhythmia, extrasystoles etc.)
- **Subjective symptoms of carditis:** increased fatigability, pains or unpleasant sensations in the heart, dyspnea, heartbeats.

- **Changes at ECG:** prolongation of PQ interval (PR), sometimes extrasystoles, displacement of ST segment, prolongation of electric systole.
Symptoms of circulatory failure may be registered.

**Pericarditis** – it may be dry or exudative (with small quantity of exudate). Appearance of pericardial murmur is possible.

**Endocarditis** is accompanied by appearance of murmurs testifying to involvement of cardiac valves into the process.
Systolic murmur reflects mitral regurgitation – the principal symptom of rheumatic valvulitis:

- as for character – continuous, blowing;
- of various intensity, doesn’t depend upon postural change and phase of respiration;
- connected with the 1st tone;
- occupies majority of the systole;
- usually is conducted in the left axillary region.
EcoCG at valvulitis of mitral valve reveals:

- Club-shaped thickening of mitral valve leaflets
- Their «shaggy-like» character
- Diminishing of their excursion
- Mitral regurgitation.
Affection of aortic valve

- It manifests with basal protodiastolic murmur, typical for aortic regurgitation:
- It begins immediately after II tone
- As for character – high frequent, blowing, diminishing
- It’s auscultated best of all along left edge of sternum after deep inspiration at forward inclination of body.
EcoCG at valvulitis of aortic valve reveals:

- Low-amplitude tremor of aortic valve leaflets
- Thickening of echo signal from leaflets
- Aortic regurgitation
Rheumatic heart disease

- They start to form after past rheumocarditis at acute or repeated rheumatic attack after 3-4 months from the beginning of attack.
- Formed rheumatic heart disease may be diagnosed in a patient after 10-12 months after beginning of rheumatic attack at presence of objective clinical and EcoCG signs of valves affection.
- Repeated rheumatic attacks increase possibility of formation of heart disease.
- Repeated rheumatic attack in patients with rheumatic anamnesis is considered to be a new episode of rheumatic fever, but not recurrency of previous attack; it manifests predominantly with carditis, more rarely – with carditis and polyarthritis, seldom – with chorea.
Rheumatic chorea

- It’s typical manifestation of ARF in 16-18% of cases, predominantly in girls of 6-16 years old.
- It’s accompanied, as a rule, by rheumocarditis or polyarthritis, rarely can be isolated.
- Duration of clinical manifestations is from 2 to 6 months.
Clinical signs of rheumatic chorea at ARF in children:

- Gradual development, the child becomes irritable, emotionally instable.
- Distal hyperkinesis are developed (bilateral jerks of muscles of trunk, extremities) which are increased at excitement and disappear during sleep. Hyperkinesis can be unilateral (hemi-chorea).
- Decomposition of movement (lurch, instability in Romberg's position, disorders of handwriting).
- Muscular hypotonia (symptom of “flaccid shoulders”), sometimes marked - Chorea mollis («soft» chorea).
- Signs of vegetative dysfunction (increased hyperhidrosis, red dermographism)
- Psychical disorders (tearfulness, depressed mood).
Ring-shaped (annular) erythema

- Manifestation of rheumatic vasculitis in children is observed rarely (5-15% of cases), although it is absolutely specific sign for β-hemolytic streptococcus of group A.
- Rash is characterized by pink-pale rings with well-defined external and less defined inner edge, with pale central part, localizes on trunk, abdomen, inner surface of arms and hips.
- Rash isn’t accompanied by itch, disappears during several days.
Rheumatic nodules

- Fine, dense, roundish, confined, painless mass, localized under skin, in fascia, aponeurosis, in periostal regions, around joint capsule, upon extensor surface of knee, elbow, and metacarpophalangeal joints, on occiput.

- They are revealed in 10% of patients.

- As a rule, they completely disappear during 1-2 months.
**Diagnostic criteria of ARF**  
Kisel-Jones (in modification APP, 2003)

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<th>Big criteria</th>
<th>Small criteria</th>
<th>Data confirming preceding A-streptococcal infection</th>
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| Carditis                      | **Clinical:**  
- Arthralgia  
- Fever  
- Abdominal pains  
- Nasal bleeding  
**Laboratory:**  
- Increased acute phase reactants—ESR, C-reactive protein.  
**Instrumental:** prolongation of PR interval at ECG, signs of mitral or aortal regurgitation.                                                                 | Positive A-streptococcal culture, isolated from throat, or positive test of quick definition of A-streptococcal antigen.  
Increase or increasing titers of anti-streptococcal antibodies (ASL-O, anti-DNA-ase B).                                  |
| Polyarthritis                 |                                                                                                                                                                                                                                                                         |                                                                                                |
| Chorea                        |                                                                                                                                                                                                                                                                         |                                                                                                |
| Annular erythema              |                                                                                                                                                                                                                                                                         |                                                                                                |
| Subcutaneous nodules          |                                                                                                                                                                                                                                                                         |                                                                                                |
Outstanding scientist-pediatrician Alexander Andreevich Kisel (1939) gave brilliant description of main manifestations of rheumatism, calling them absolute symptom complex of the disease. Time showed the relevance of this symptom complex in diagnostics of ARF, they received name “main criteria”. Polyarthritis, carditis, and chorea can proceed independently, but more often – in different combinations with each other.
Small criteria

- **Arthralgia** – migratory pains in big joints of different intensity, not accompanied by pain on palpation and other symptoms of inflammation.

- **Fever** – increase of temperature more than 38\(^\circ\) C at absence of other causes.

- **Increase of acute phase reactants** (at absence of other causes) – ESR more than 20 mm/h, C-reactive protein twice more than norm.

- **Prolongation of PR** on ECG (more than 0.2 sec) revealed for the first time (at absence of other causes).

- **Signs of mitral or aortal regurgitation at EcoCG** revealed for the first time (at absence of other causes), not less than in 2 examinations with interval 10-14 days.
Criteria of activity of rheumatic process

- **High activity** (III degree): endomyocarditis, pericarditis, polyarthritis, pneumonia. Laboratory indices: neutrophilia 10-12x $10^9/l$, ESR more than 40 mm/h, CRP +++ - ++++ (or twice more than norm), α2-globulins more than 13-14%, γ-globulins more than 25%, seromucoid more than 6-10 U, DFA – 0.25-0.5 U, sialic acids more than 0.500 U, ASL-O and ASK – 3-5 times more than norm.

- **Moderate activity** (II degree): moderate clinical manifestations (carditis, subfebrile temperature, polyarthritis or polyarthralgia). Laboratory indices: neutrophilia up to $10^9/l$, ESR 20-30 mm/h, CRP + - ++ (or more than 6 U), α2-globulins 11-13%, γ-globulins 22-25%, seromucoid more than 6 U, DFA – 0.25-0.3 U, sialic acids more than 0.400 U, ASL-O and ASK – 1.5-2 times more than norm.

- **Minimal activity** (I degree): minimal symptoms of carditis. Laboratory indices are normal or some of them are slightly increased.
Classification of rheumatic fever (APP, 2003)

- Acute rheumatic fever
- Repeated rheumatic fever

Clinical variants:

Clinical manifestations:

Main:
- carditis
- arthritis
- chorea
- annular erythema
- rheumatic nodules

Additional:
- fever
- arthralgia
- abdominal syndrome
- serosites
- nasal bleeding

Course of ARF:
- acute
- subacute,
- lingering
- persistent recurrent
- latent
Outcome:

- Convalescence
- Chronic rheumatic heart disease:
  - Without valvular affection*
  - With valvular affection **

Stages of CI:

CSV*** NYHA****
CI I FC II-I
CI IIA FC III-II
CI IIB FC IV-III
CI III FC IV

* Presence of post-inflammatory marginal fibrosis of valvular leaflets without regurgitation is probable.
** At presence of primary revealed acquired valvular disease it’s necessary to exclude other causes of it’s formation (if possible).
*** By classification of N.D.Strazhesko and V.H.Vasilenko.
**** Functional classes by NYHA (New York association of cardiologists)
1. Treatment at a hospital

1.1. **Motion regimen.** Bed rest or semi bed rest for 2-3 weeks with its step-up after disappearance of inflammatory process, laboratory activity indices and signs of cardiac insufficiency.

1.2. **Diet.** With limitation of salt (3-4 g/day) and liquid, enriched with potassium, magnesium and vitamins.

1.3. **Etiotropic treatment.** Benzyl penicillin sodium (penicillin G) 50-100 000U/kg/day divided into 4-6 injections during 10-14 days. Later on – injections of long acting penicillins: benzatin benzyl penicillin (retarpen) 600 000U (if body weight is less than 27 kg), and 1 200 000U (if body weight is more than 27 kg) i.m. once in 3-4 weeks. At allergic reaction for penicillin macrolides are prescribed: azithromycin 10 mg/kg on the first day, afterwards 5 mg/kg during 2-5 days or clarithromycin 15 mg/kg divided into 2 intakes during 10 days.

At allergic reaction for macrolides cephalosporins (cephalexin, cefutil) or lincosamides (lincomycin, clindamycin) orally in age-dependent doses during 10 days are prescribed.
1.4. Pathogenetic treatment

1.4.1. Courses of **NSAIDs** (diclofenac sodium 2-3 mg/kg/day, ibuprofen 5-10 mg/kg/day during 2-3 months) are prescribed.

1.4.1.1. At absence of valvulitis, carditis, polyarthritis, moderate or minimal activity (I-II degree) of inflammatory process **NSAIDs** are prescribed during 3-5 months instead of GCS. Untimely withdrawal of anti-inflammatory therapy can lead to development of rebound syndrome (exacerbation of the disease without repeated streptococcal infection).

1.4.2. **Glucocorticoids.** At presence of severe carditis with involvement of mitral (aortic) valves, exudate in pericardium cavity, polyserosites, high activity (II-III degree) of inflammatory process **glucocorticoids** (prednisolon 1mg/kg/day) during 3-4 weeks with gradual decrease of the dose after normalization of laboratory indices of inflammatory process’ activity are prescribed. It’s withdrawal is possible not earlier than in 1.5-2 months from the beginning of the therapy.
1.4.3. At development of **congestive cardiac insufficiency** cardiac glycosides (digoxin), diuretics (furosemide, veroshpiron), adrenoblockers (propranolol, atenolol, corvitol), cardioprotectors, inhibitors of ACE (but not simultaneously with NSAIDs) are used.

1.4.4. Intake of **haloperidol** (0.5-1.0 mg/kg/day with increase of the dose by 0.5mg every 3 days if necessary, but not more than 5mg/day), **valproate sodium** (15-30mg/kg/day), i.v. injection of immunoglobulins, vitamins of group B, phenobarbital is recommended for treatment of rheumatic chorea.
II stage – consolidation of reached progress in specialized children’s cardiorheumatic sanatorium.

III stage – prophylactic measures.

Primary and secondary prophylaxis are distinguished.

Primary prophylaxis means: timely and correct therapy of streptococcal infection’s episodes (pharyngitis, acute tonsillopharyngitis, scarlet fever, exacerbation of chronic tonsillitis), usage of antibiotics of penicillin group (penicillin, ospamox, amoxicillin, augmentin), cephalosporin group (cefalexin, cefutil), macrolides (azithromycin, clarithromycin, rovamycin) minimum up to 10 days; sanitation of foci of chronic infection in nasopharynx; tempering; valid nutrition.
Secondary prophylaxis is realized by regular injections of penicillins of prolonged actions – bicillin-5 or benzathine benzylpenicillin (retarpen) in following doses:
- 600 000 U, if body weight is less than 27 kg
- 1 200 000 U if body weight is more than 27 kg i.m. once in 3-4 weeks

At allergy for penicillins secondary prophylaxis is carried out with courses of macrolides – 20 days of every month.
Duration of secondary prophylaxis:
- at ARF without rheumocarditis and chorea – up to 21 years, but not less than 5 years;
- at rheumatic attack with rheumocarditis and valvulitis but without formation of acquired heart disease – up to 25 years, but not less than 10 years;
- at presence of formed acquired heart disease – up to 40 years old;
- for patients with valvular defect and for those who underwent surgical correction of heart disease WHO experts recommend to carry out secondary prophylaxis all life long.
During secondary prophylaxis it’s obligatory to carry out so called **current prophylaxis of rheumatic fever** – prescription of antibiotics (which streptococcus is sensitive to) for all patients who have passed ARF, at intercurrent infectious diseases and small surgical interventions (e.g., tooth extraction) in therapeutic doses during 10 days.
Thank you for your attention!