Fourth practical training

TOPIC:

Occupational allergic diseases

for students majoring in Medicine 3rd year,
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BRONCHIAL ASTHMA

Definition

Bronchial asthma (BA) is heterogeneous disease, which is characterized by chronic inflammation of the airways and is determined by a history of intermittent severity of respiratory symptoms (wheezing and / or tightness in the chest, shortness of breath and cough) and intermittent bronchial obstruction (expiratory dyspnea). (GINA, Revision 2014) .

Phenotypes of asthma:

- Allergic asthma ;
- Non-allergic asthma ;
- Late onset asthma ;
- Asthma with fixed obstruction ;
- Asthma and obesity .

Classification of BA:

- Atopic ;
- Non-atopic ;
- Mixed ;
- Occupational ;
- Syndromic .

The non-atopic asthma is a diverse group, including the following forms:

- Non-atopic allergic ;
- Non-atopic non-allergic ;
- Idiopathic .

In non-atopic non-allergic asthma, depending on the factors and mechanisms that provoke the manifestation of symptoms, the following forms can occur: exercise-induced asthma, asthma after viral and bacterial infections, autoimmune, drug-induced. Drug induced asthma can be the aspirin asthma (asthma from intolerance to aspirin or other non-steroidal anti-inflammatory drugs combined with chronic rhinosinusitis and nasal polyposis, the so-called triad asthma).

Etiology and pathogenesis of BA

It has been established that BA can be caused by a number of sensitizing factors from the external and internal environment, known as **indoor** and **outdoor** allergens,

among which the most important are pollens, dust mites, molds, pet allergens. Factors related to increased non-specific bronchial reactivity are dust, cigarette smoke, unburned gases from motor vehicles (diesel particles), chemicals, cosmetics, fragrances, disinfectants and others. Allergy is the basis for the development of hypersensitivity in 80-90% of children and 50-60% of adults. The inflammatory component has been suggested as a cause of bronchial obstruction in studies and theories by a number of authors (ST Holgate, 1993). Chronic allergic bronchitis is considered a cornerstone in modern understandings of the pathogenesis of asthma. It is an integral part of the international and national consensus on the disease (International Consensus on the Diagnosis and Treatment of Asthma since 1997, GINA revisions in 2006 and 2014) .

Asthma is a disease characterized by chronic allergic inflammation of the airways due to the following several components: cells, mediators and mechanisms of immune inflammation. The main cells of allergic inflammation are mast cells, eosinophils, tissue basophils (replacing eosinophils in the nasal mucosa) and helper lymphocytes (T h) of subclass 2.

Modern interpretation of the pathogenesis of the disease is impossible without understanding the concept of Mosmann , which is based on the concept of the so-called Th 1 and Th 2 immune response.The theory is that there is a presence of two subpopulations of helper s(CD4 +) T lymphocytes- Th 1 and Th 2 .

The Th 1 subpopulation is identified with cytotoxic T-Ly (CTL) and T-lymphocytes that mediate the so-called delayed type of hypersensitivity. The Th 2 subpopulation is identified with helper-induced CD4 + T cells, which are involved in stimulating the humoral immune response. After that, each of these two subpopulations of T lymphocytes binds to a specific cytokine profile. The Th 1 immune response binds to and is determined by type I, known as the cell-mediated cytokine profile, and the Th 2 immune response by type II , which includes cytokines and interleukins related to humoral immunity. Certain cellular subpopulations and cytokines correspond to each type (Th 1 and Th 2) immune response.

We come to the conclusion that each type of immune response mediates and causes a certain type of disease - autoimmune, allergic, infectious.

In Th 1 infections , the immune response provides protection against intracellular parasites. The Th 1 (cell-mediated) immune response is also involved in the pathogenesis of organ-specific autoimmune diseases, while the Th 2 immune response is involved in the pathogenesis of systemic autoimmune diseases. Th 2 immune responses have been shown to be predominant in atopic asthma , as evidenced by the presence of Th 2 -type cytokines and eosinophils,with elevated IgE levels in the bronchoalveolar lavage.

It is also known that the Th 2 immune response plays a protective role in pollinosis and atopic dermatitis.

It can be concluded that Th 1 and Th 2 - lymphocyte subpopulations are involved in maintaining the delicate balance between infectious and immuno-allergic diseases,

and the prevalence of one or the other type determines the dominance of the pathology.

In atopic allergic diseases,like in atopic bronchial asthma, Th 2 immune response predominates while Th 1 immune response is considered by some authors to be protective (Le Messuirer H., 1995).

According to a number of researchers, the protective or pathogenic role of one of the two types of immune responses - cell-dependent or antibody-dependent, allows to regulate to some extent the balance of Th 1 and Th 2 cells and their cytokine profile or "redirect" the immune response in the desired direction. In recent years, special attention has been paid to therapeutic strategies aimed at redirecting the prevalent Th 2 -mediated immune response in allergic diseases to the cell-mediated Th 1 immune response. This is Romagnani's "new immunotherapeutic strategy for atopic diseases" of 1998.

The predominant share of cell-dependent (Th 1 -mediated) immune response among people in developing countries also explains the lower prevalence of atopy compared to industrialized countries (Okudaira, H., 1998).

Studies on the pathophysiological factors and pathogenetic mechanisms of BA provide ways to distinguish between two types of allergic inflammation, each of them is mediated by a specific type of cells and mediators - acute and chronic. Acute inflammation is an expression of an early allergic reaction of the rapid type, which is based on mast cells and mediators released during degranulation. Chronic allergic inflammation is an expression of a late IgE mediated immune response. The leading pathophysiological manifestation of acute inflammation is bronchospasm, and in chronic inflammation - increased nonspecific bronchial reactivity. As a consequence of unsatisfactory therapeutic control and ineffective response to chronic allergic inflammation in the bronchi is the appearance of irreversible bronchial obstruction leading to airway remodeling.

Clinical symptoms of BA*:*

- Shortness of breath;
- Cough;
- Whistling breathing;
- Daggers and / or weight in the chest.

According to the clinical course of BA, there are acute and chronic forms. Both the first attack and the subsequent exacerbations (asthma attacks) are interpreted as acute asthma .

Chronic asthma, depending on the degree and severity of clinical symptoms and the parameters of lung function, is intermittent and persistent.

Table 1 shows the classification of chronic asthma, in accordance with generally accepted criteria for the severity of the clinical picture and indicators reflecting lung function.

Table 1. Chronic asthma - classification according to the clinical picture and spirometric indicators

Degrees (forms) of asthma	Clinical picture	PEF and _ FEV 1.0
Intermittent (episodic)	Rare attacks, once a week. The patient has no asthma symptoms between the attacks. Up to 2 episodes of nocturnal dyspnea and wheezing per month	PEF - normal between seizures PEF is = or > 80% of provided for the patient value. Daily PEF fluctuations are < 20%
Persistent light	Attacks occur more than once a week, but less than once a day Over 2 episodes of nocturnal dyspnea and wheezing per month Symptoms 1-2 times per week Symptoms during the night 1-2 times per month Mild symptoms between attacks	PEF is = or > 80% of what is predicted for the patient, and daily fluctuations vary between 20-30%
Moderate (moderately severe)	The attacks are daily The use of SAB2-agonists increases The episodes of nocturnal dyspnea and wheezing are more than once a week It impairs the patient's physical and social activity	Deteriorated spirometric indicators PEF is 60-80% of envisaged for the patient value. Daily fluctuations of PEF with > 30 %
Heavy	Persistent attacks, severely limited physical capacity, frequent asthma attacks at night, frequent hospitalizations	PEF < 60% of that envisaged for the patient with daily fluctuations above 30% despite treatment

To assess the severity of asthma attacks are accepted certain clinical and functional criteria included in various schemes and scales.

One of the most used in practice is that of the British thoracic It is based on an assessment of the severity of clinical manifestations and the values of key indicators of lung function. The clinical symptoms assessed are the frequency of breathing per minute and the patient's ability to have a normal conversation, which assesses the degree of respiratory fatigue. From the functional lung and heart parameters, the heart rate and peak expiratory flow values (PEF) in l / s are recorded as a percentage of those predicted for the patient. Based on the

above clinical and functional criteria, the severity of an asthma attack is assessed as mild, moderate, severe and life-threatening.

Severe and life-threatening asthma attacks are associated
with the condition of asthmatic status or severe acute asthma.This is critical
life-threatening asthmatic condition in which clinical,
physical, functional and gasometric data for rapidly progressing
respiratory failure with development of severe dyspnea at rest, cyanosis, respiratory fatigue, "quiet lung", to which are added the signs of right-sided heart failure.

The most common triggers for asthmatic status are massive exposure to allergens, viral infections, unreasonable and abrupt discontinuation of long-term treatment with systemic steroids.

Occupational bronchial asthma (OBA)

Definition

Occupational bronchial asthma is bronchoallergosis, which is characterized by a relapsing course. The disease is characterized by spontaneous or pharmacologically induced reversible bronchial obstruction. The leading factors and mechanisms in the pathophysiology and pathogenesis of asthma are associated with atopy and increased nonspecific bronchial reactivity, and the activity of allergic inflammation - with the predominance of inflammatory over anti-inflammatory mediators involved in the cellular and cytokine profile of inflammation.

Characteristic of occupational bronchial asthma is that the factors of the working environment are crucial for allergic inflammation and bronchial hyperreactivity.

Etiology

The most commonly known causes of PBA can be divided into two groups: biological substances containing protein components with the quality of complete antigens and low molecular weight chemicals. The substances of the second group act as incomplete antigens (haptens) or irritants.

According to the mechanism of action, occupational allergens are divided into three groups. The first group includes substances with proven and known sensitizing potential such as drugs, bioproducts, enzymes, pollen and others. The second group includes substances with a complex mechanism of action. They have an allergenic, irritating and pharmacological effect. Organic powders, salts of heavy metals (chromium, nickel, platinum), organic solvents, formaldehyde, pesticides, paints, varnishes, isocyanates, plastics and others act on this mechanism. The third group includes substances with irritating, toxic or toxo-allergic effects on the bronchi such as inhalation of gases, smoke, vapors and aerosols of chlorine and sulfur compounds, vapors of acids and bases, ammonia, exposure to quartz dust and others **.**The dust from some hard metals,may have not only fibrogenic but also sensitizing effect has

been proven, such as beryllium, tungsten, chromium, nickel, cobalt, aluminum and others.
The incidence of asthma varies from industry to industry. For example, in industrial detergent activities, the inhalation of certain enzymes (used to produce washing powder) leads to the development of symptoms in some of the exposed workers. About 5% of people working with laboratory animals or latex gloves develop asthma. Isocyanates are chemicals widely used in many industries including painting, production of plastics and foam. These chemicals can cause asthma in nearly 10% of exposed workers.
Irritants in high doses can also cause asthma. These are hydrochlorides, sulfur dioxide or ammonia, which are found in the oil and chemical industries.
The type and nature of exposure is important in cases of asthma with occupational etiology. This type of asthma usually develops after exposure to work-related substances for months or years.
Workers in the laundry detergent industry may develop an allergy to *Bacillus subtilis enzymes* , while bakers may develop allergies and asthma when exposed to various flours (World Allergy Organization).
Occupational groups with a higher risk of developing asthma according to the World Allergy Organization are:

- Veterinarians, fishermen and laboratory workers may develop allergic reactions to animal proteins;
- Healthcare professionals may develop asthma after inhaling latex glove powder or mixing powdered medications;
- Workers exposed to repeated exposure to small molecules in the air. These are found when working with plastics and resins.

The pathogenetic mechanisms of OBA are quite complex and diverse. In summary, according to the pathogenesis, the following forms of occupational bronchial asthma are distinguished:

- immuno-allergic reaction with Antigen – Antibody;
- pharmacodynamic (histamine liberalization);
- reflex type with direct irritation of the bronchi receptors;
- blockade of B2-adrenergic bronchial receptors.

Classification of OBA:

1. Allergic.
2. Non-allergic.
3. Mixed.

Characteristics of the forms of OBA:
The allergic form can appear at the first contact of the worker with the allergen from the working environment to which he is sensitized. In atopics, a latent period is not

required to sensitize the body. Non-atopic individuals require different lengths of time to sensitize to the relevant occupational allergen. The duration of this period usually varies from a few days to a month. Atopic BA is mediated by IgE and IgG 4 , and non-atopic BA is mediated by IgG and IgM. OBA can develop gradually while there is other occupational lung diseases such as pneumoconiosis, chronic bronchitis, etc.). The disease can occur secondarily and as a consequence of frequent broncho-pulmonary infections plus the exposure to an occupational allergen or substance from the work environment with sensitizing potential .

Asthma that is irithative is more common in the chemical, oil and oil refining industries, as well as in the field of powder production of inert or toxic gases, aerosols, vapors and others.

The mixed form of asthma is the most common one in the clinical practice. That is a combination of allergic, irritant and neuro-reflex pathogenetic mechanisms. It is associated with the influence of complex and diverse pathogenetic effects that most substances in the work environment have.

Typical examples for this are isocyanates. They have a complex effect on the bronchi in which several mechanisms come together: irritative, through functional blockade of B2 receptors and formation of reactive N-CO groups. The latter are characterized by increased affinity for the amino groups of human proteins, as a result of which isocyanate-hapten becomes a complete antigen.

Diagnostic algorithm:

Includes two stages: the first requires the diagnosis of BA, and the second - to specify the occupational etiology of the disease. Expert assessment of asthma includes the following aspects:

1. Specifying the type of asthma:
   - with a predominant allergic component;
   - non-allergic;
   - mixed;
   - with occupational etiology;
   - exercise-induced asthma;
   - idiopathic;
   - another.
2. Specification of the clinical form:
   - debut (first attack);
   - episodic (intermittent);
   - chronic (persistent) asthma - exacerbation, with unsatisfactory or good therapeutic control.
3. In asthma attacks, the severity of the attack should be specified in accordance with established clinical practice criteria.
4. Specify the degree and severity of persistent asthma in accordance with GINA criteria .
5 . Expertise of the ability to work according to the current legislation in our country.

Medical history

Typical for asthma are:

- More than one symptom (wheezing, shortness of breath, cough), especially in adults;
- Worsening of symptoms at night or early in the morning ;
- Symptoms vary over time and severity ;
- Triggers: viral infections and non-specific factors .

Unusual symptoms:

- Isolated cough without other respiratory symptoms ;
- Chronic sputum production ;
- Shortness of breath associated with dizziness, nausea or paresthesias ;
- Chest pain ;
- Exercise-induced dyspnea with noisy inhalation .

Proof of reversible bronchial obstruction:

- Documented significant variability in lung function and documented bronchial obstruction ;
- In case of low FEV1, at least once during the diagnostic process to confirm that FEV1 / FVC is reduced (normal> 0.75-0.80 in adults,> 0.90 in children).

Diagnosis of certain populations:

- Patients that only have cough as a clinical symptom (the following conditions are considered in the differential diagnosis): cough form of asthma induced by cough medication - ACE inhibitors,, gastroesophageal reflux disease, posterior nasal flow syndrome, chronic sinusitis, laryngeal dysfunction);
- Occupational asthma and worsening work environment asthma ;
- Ahletes ;
- Pregnant women (the bronchial provocation tests shouldn`t be done and the control therapy should be reduced) ;
- Old age (cardiovascular diseases, left heart failure, ACOS should be excluded as provoking respiratory symptoms) ;
- Smokers and ex-smokers (DD: ACOS) ;
- Obesity .

Diagnosis of patients who have started control therapy - in 25-35% of patients diagnosed with asthma in primary care, the diagnosis is not confirmed.

Modern diagnostic algorithm depending on symptoms and lung function

Objective condition	Stages to confirm the diagnosis
Variable respiratory symptoms with variable obstruction	If the diagnosis is confirmed - to assess the degree of control and treatment of asthma
Variable respiratory symptoms without variable obstruction	Bronchial provocation test should be repeated after stopping bronchodilators (SABA after the 4th hour, LABA> 12 h) or during symptoms: Norm - alternative diagnosis; FEV1 > 70 % of the planned - to perform a bronchial provocation test. In case of negative BPT , the patient's condition should be reassessed after 2-4 weeks; FEV1 <70 % of predicted follows a step up in the therapy for 3 months and reassessment of symptoms and lung function. If there is no good clinical response to the therapy, return to the old treatment and the patient is referred for further research.
Few respiratory symptoms, normal lung function, no variable obstruction	Repeat BPT after stopping bronchodilators or during available symptoms: Norm - alternative diagnosis; A step down is taken in the control therapy: When symptoms appear and lung function declines, the diagnosis is confirmed. Therapy is adjusted by a "step up" to the previous lowest effective dose; If there is no change in the symptoms or lung function of the lowest control step - stop therapy and follow up the patient for a period of 12 months.
Persistent shortness of breath and fixed bronchial obstruction	"Step up" for a period of 3 months, reassessment of symptoms and lung function: In the absence of a response - return to previous therapy and refer the patient for additional tests; ACOS should be considered in the differential diagnosis plan.

The specificity of the diagnosis and expert assessment of OBA is to clarify the occupational etiology.

The etiological diagnosis aims to establish the causal relationship of asthma with the occupation based on the following criteria:

- occupational hygiene (objectifies occupational contact with allergens and irritants);
- epidemiological (collective test) for the frequency of allergic workers in a specific workplace;
- occurrence of asthma after starting work;
- presence of bronchial hyperreactivity ;
- positive exposure and elimination test.

In allergic asthma there are additional criteria proving sensitization to occupational allergens:

- positive skin allergy tests;
- positive broncho-provocation tests;
- positive immunological tests .

Peculiarities in the interpretation and expert evaluation of some diagnostic methods in OBA:

1. In atopic individuals, the length of service is not essential for the onset and manifestation of occupational asthma.
2. The elimination test is positive only in the stages of asthma preceding the remodeling of the bronchial tree.
3. The collective (epidemiological test) is characterized by high reliability in assessing the occupational etiology of the disease.
4. The tests for specific IgE antibodies against occupational allergens and bronchoprovocation tests with such have high sensitivity and informativeness, but are difficult to implement in practice due to the complex and difficult process of standardization of occupational allergens, labor intensity and risk, and their high cost.
5. The labor-expert assessment of the disease must take into account the individual characteristics and reactivity of the organism, as well as the role of other factors outside the work environment.

Hypersensitivity pneumonitis (HSP)

Definition

Hypersensitivity pneumonitis (HSP) is an immune inflammation of the lung parenchyma involving the alveoli and interstitium caused by inhalation of bacteria, molds and organic dusts. Etiological factors are found in the

environment, most often due to occupational exposure and the action of certain allergens. It is also called "exogenous allergic aleveolitis ".

Frequency

No epidemiological studies have been conducted in Bulgaria. The disease is considered occupational . It is estimated that about 4% of farmers, 20% of people raising different species of birds and 25-70% of those using contaminated air conditioning systems and humidifiers suffer from it.

Etiology

HSP is an allergic inflammation that affects the alveolar wall, the interstitium, and in some cases the most peripheral parts of the bronchioles. Therefore, it is mainly a parenchymal disease, most often of an occupational nature and occurs under different names: farmer's lung, miller`s lung ,coffee worker`s lung and others.
According to one of the etiological classifications (Khomenko AG et al.) HSP can be caused by:

- microorganisms / thermophilic fungi, Gram-negative bacteria, or algae;
- biologically active substances of animal and plant origin (proteases, glyco and lipoproteins, polysaccharides, enzymes);
- low molecular weight compounds (drugs, isocyanates, metal salts).

The main causes are various bacteria and molds that grow on organic matter in industrial production and agriculture. The most common allergens and diseases they cause when inhaled are presented in Table 1 below.

Table 1. Mechanism of action of occupational allergens on the respiratory tract.

FACTORS / AGENTS /	MECHANISM OF ACTION	TYPE OF PULMONARY INJURY
1. MEDICTIONS / ANTIBIOTICS, SULPHONAMIDES, VITAMINS, AMINAZINE /, SOME TYPES WOOD POWDER,	SENSITIZING EFFECT	BRONCHOSPASTIC SYNDROME
2. CHROME, NICKEL CHLORIDE, CHLORAMINE, URSOL, FORMALDEHYDE, POWDER / FROM COTTON, TOBACCO, CEMENT /, ELECTROWELDING AEROSOLS.	1. SENSITIZING EFFECT. 2. LOCAL IRRITANT ACTION. 3. PULMOFIBROSIS.	1. BRONCHOSPASTIC SYNDROME. 2. INITIAL INJURIES OF THE RESPIRATORY TRACT BY THE TYPE OF CHRONIC TOXIC OR POWDER BRONCHITIS, TOXIC PNEUMOSCLEROSIS, PNEUMOCONYASTOSIS WITH SUBSEQUENT DEVELOPMENT OF ASTHMA
3. CHLORINE, FLUORINE, IODINE AND CONTAINING COMPOUNDS, NITROGEN OXIDES, VAPORS OF ACIDS AND BASES, POWDER / VARIOUS SILICATES, CARBON, GRAPHITE, GRAPHITE, GRAPHITE, IRON,ALUMINIUM.	1. IRRITATIVE EFFECT. 2. PULMOFIBROSIS.	1. CHRONIC TOXIC BRONCHITIS. 2. POWDER BRONCHITIS. 3. TOXIC PNEUMOSCLEROSIS. 4. PNEUMOCONIOSIS.THE ASTHMA IN THESE CASES IS A COMPLICATION OF THE MAIN OCCUPATIONAL PULMONARY DISEASE.

Table 2. The most common inhaled allergens of animal, plant and chemical origin in the etiology of HSP. Occupations at risk.

Origin and type	Endangered professions
A. Animal allergens / hair, dandruff /	
1. Of people	Hairdressers
2. Of animals: - Cattle, sheep, dogs, cats, goats, rabbits, guinea pigs, mice,	Livestock breeders, zoologists, upholsterers, carpet weavers, experimenters, veterinarians, foresters, hunters
- Hermelin, beaver and others.,hides and skins	Furriers, hunters, traders, poultry farmers
- Birds	Pigeons
- Snakes and their venom, ticks	Zoologists, biologists, laboratory technicians
- Insects / dust and odor /, including wheat beetle	Beekeepers, flours, zoologists, poultry and animal breeders, bakers, millers, silk spinners
- Pearl powder	jewelers, button makers
- House dust and house tick	Maids

Origin and type	Endangered professions
B. Plant allergens / powders /	
1. Cotton, linen, hemp, jute, sisal.	Weavers, textile workers, upholsterers, seamstresses, rope makers, packers
2. Powder of wheat, hay, straw, malt, alfalfa.	Livestock breeders, foragers, malt workers.
3. Flour and gluten in them.	Bakers, millers, farmers, malt workers.
4. Raw coffee and cocoa.	Loaders, bakers and coffee sellers.
5. Castor seed.	Workers in oil mills, farmers.

6. Beech, walnut and dust from exotic trees / rosewood, mahogany, etc.	Carpenters, parquet makers, furniture makers, veneers.
7. Arabic rubber.	Printers, hairdressers.
8. Essential oils / cosmetics, perfumes, spices / .	Hairdressers, beauticians, drugstores, spice grinders .
9. Proteases / bacterial enzymes /.	Workers in detergent factories and public laundries.

Origin and type	Endangered professions
B. Plant allergens / powders /	
10. Latex	Medical staff / surgeons, orthopedists, etc. operative specialties, nurses /, dentists, laboratory assistants, workers in the production of latex products for medicine and everyday life / latex gloves, catheters, raincoats, pacifiers, balls, balloons, rubber toys, paints, etc./
11. Tobacco mold / *Aspergillus sp p.* /	Tobacco workers.
12. Contaminated with *Bacillus subtilis* and *Alternaria* powder.	woodworkers and wood processing.
13. hay powder contaminated with *Thermoactinomyces , Aspergillus sp p. , Penicillium s p p . , Candida*	Agricultural workers, farmers, etc. FARMER`S LUNG
14. Moldy pressed sugar cane / bagasse /, contaminated with *T. sacchari , T. _ vulgaris .*	Agricultural workers, farmers, etc.
15. Thermoactinomyces, *Penicillium, Candida spp., Cephalosporium spp., Klebsiella spp.*	"VENTILATION LUNGS" Operating and users of contaminated ventilation systems, humidifiers and central heating.

16. Inhalation of dust, contaminated with *Cephalosporium sp p.* , *Penicillium sp p.* .	BASEMENT LUNGS Working in contaminated basements.
17. Rotten wood powder, contaminated with *Serpula Lacrymans, Aspergillus fumigatus* and others.	ALLERGIC ALVEOLITE OF THE "OLD HOUSE" - staff serving holiday homes, stations, chalets and hotels.

* supplemented and expanded version of " Alergology - principles and practice", MI "ARSO", 1999, 329

Pathogenesis

Allergens are inhaled as an aerosol or particles and can reach the alveoli if their size is less than 3 microns. Ig E antibodies have been shown to play no role in the pathogenesis of HP. Unlike atopy, allergen exposure here should be massive or prolonged. The proven initially precipitating IgG antibodies to thermophilic actinomycetes have long supported the thesis of an Arthus-type / immunocomplex or III-тиimmunopathological mechanism pulmonary response , with the development of vasculitis at the alveolar wall level. Subsequently, serum precipitating antibodies were found to correlate with allergen exposure and not necessarily with pathological changes in the lung. Data from pathoanatomical studies, animal experiments and bronchoalveolar lavage studies are gradually accumulating , which are evidence of a complex pathogenic mechanism in the leading role of cell-mediated immune inflammation / type IV allergic reaction . Crucial in this regard is the finding of granulomas in the interstitium between the alveoli in subacute and chronic forms of the disease - a characteristic feature of cell-mediated inflammation . Today it is believed that immune complexes play a minimal role, especially in acute HP occurring reaction 4 - 6 hours after inhalation of the allergen and remission after 24 hours.

Clinical picture

In the acute form, the complaints begin 4 - 8 hours after inhalation of a high dose of allergen and the symtoms are: cough, shortness of breath, fever up to 39 ° C accompanied by chills. The disease resembles an " acute овк ", but 2 4

hours later the complaints disappear if the contact with the allergen is interrupted (eg at the end of the working week). During the acute reaction , bilateral crepitations in both lungs and sometimes dry wheezing are found on auscultation, but a finding may be missing.
The subacute form begins a few weeks after the allergen exposure and is characterized by cough, shortness of breath and weight loss. Shortness of breath gradually increases, and cyanosis may occur.
The chronic form is observed with prolonged contact, even with a low dose of the allergen , tht form can be seen in people that are taking care of birds . Symptoms include progressively worsening dyspnea, even at rest (interstitial fibrosis and right heart failure), chronic fatigue, and weight loss. Auscultatory crepitations decrease and / or disappear, but the expiration can be prolonged.

Functional examination of respiration in the acute phase reveals a reversible restrictive defect and reduced diffusion capacity. PaO_2 is reduced. In the chronic phase , the restriction is irreversible, and some obstruction due to obliterating bronchiolitis can be observed .
Radiologically , in acute forms, bilateral small spotted infiltrates can be found , while in the chronic stage, extensive infiltrates with or without nodules are seen .

Laboratory tests

In the acute phase, mild leukocytosis may be detected. Eosinophilia is not typical, and erythrocyte sedimentation rate is normal or slightly accelerated .

Immunological tests:

1.Precipitating IgG antibodies proved by by Uchterloni immunodiffusion . The positive result should not be overestimated, as it indicates more prolonged exposure to the allergen than the presence of the disease itself.

2. In the presence of precipitins in serum, normally the intradermal skin samples are positive . ^{Papules} and erythema appear at 4-6 hours with a peak at $^{6-12}$ hours and disappear after 24 hours. The diagnostic value of the skin test in the case of precipitins is minimal .

3. The bronchial provocation test with allergen has the highest sensitivity and specificity, but is dangerous and requires observation of the patient for at least 24 hours after its implementation . Reversible restrictive defect / decrease in FVC, FEO1 and diffusion capacity was found in parallel with the increase in temperature and leukocytes in the peripheral blood starting at 4-6 hours, ^{peak} at 10 ^{hours} and recovery at 24 ^{hours} . The differences with the late asthmatic reaction are that in the latter there is a reversible obstruction / decrease mainly in FEV1 /.

4. An alternative to inhalation provocation is workplace provocation, which is easier to do but also requires 24 hours of patient monitoring.

Complications

Chronic forms lead to respiratory failure and the development of pulmonary heart disease.

The diagnosis is based on two sets of criteria:

1. General criteria - they diagnose the disease itself.

The data from the general and directed allergological anamnesis come into consideration. HP should be considered in any patient with frequent "colds" and pneumonias of unclear etiology, "idiopathic" pulmonary fibrosis and unexplained pulmonary infiltrates on X-ray.

The diagnosis is supported by paraclinical, functional, pulmonary, and immunological results.

2. Specific criteria - through them the professional etiology of the disease is objectified.

The needed research includes the following diagnostic procedures:

- detailed professional anamnesis;
- data from the occupational characteristics and the performed study for occupational disease, which should describe in detail the professional route of the patient, the specifics of the profession, the available risk factors from the working environment for which there is objective evidence, laboratory tests by licensed laboratories. The latter objectify the presence of the respective inhaler allergen to which the person is occupationally exposed, etc .;
- results of the performed imaging, functional lung, immunological and histo-morphological examinations;
- a positive elimination test, which is valid for the acute form of the disease;
- a positive collective (epidemiological test) proving a higher incidence of HSP workers occupationally exposed to the same type of inhaled allergens and substances.

Differential diagnosis

In the acute stages should be made with "cold" or flu: frequent pneumonia and atopic / exogenous / bronchial asthma.

Table 3. Differential diagnosis between exogenous bronchial asthma and exogenous allergic alveolitis.

Criteria	Asthma	Allergic alveolitis
Family history of atopy	Yes	no
Localization of the process	small bronchi and bronchioles	alveoli and interstitium
Beginning after contact with the allergen	immediately	4-8 hours in the acute form
Auscultation	dry wheezing	crepitation
X-ray	no changes	small spotted infiltrates
Spirometry	obstruction	restriction

Antibodies in serum	increased Ig E	precipitating - Ig G

The distinction from *allergic bronchopulmonary aspergillosis* is difficult, but the precipitins and Arthus-type skin reactions to Aspergillus can help us with the differential diagnosis.When they are positive we may see a case allergic bronshopulmonary aspergillosis. The following criteria are important as well:

1. Asthmatic attacks
2. Eosinophilia in the peripheral blood
3. Positive skin reaction to the allergen
4 . Elevated serum Ig E
5. Central bronchiectasis
6. Proof of A. fumigatus in sputum

In *the chronic stage , the* differential diagnosis is made with pulmonary - interstitial fibrosis of another etiology.

Treatment

The first measure is to stop contact with the suspected occupational allergen. Sometimes this is enough, especially in mild acute forms of HP .

The acute form of HP is treated with prednisolone 40 - 60 mg. orally with dose reduction depending on the effect achieved and total duration 2 - 4 weeks . *The* chronic form with advanced pulmonary fibrosis and respiratory failure is treated as complex as pulmonary interstitial fibrosis, but prednisolone is added at the same dose. Inhaled corticosteroids (ICS), unlike asthma, are not effective here. In case of respiratory and cardiac complications, oxygen and cardiotonic treatment is added, and the patient's ability to work is determined by TEMC or NEMC.