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Causes of failures in the treatment of asthma in children. Establishment of an new integrative therapeutic program

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ABSTRACT

Asthma remains one of the most common chronic respiratory diseases in children with a high incidence rate, its continued growth, and patient disability, which defines asthma as a serious medical and social problem. Despite significant advances in asthma diagnostics and treatment over the past decades, more than half of patients receiving modern therapy do not have disease control. It is necessary to thoroughly study the causes of this phenomenon and develop new diagnostic and therapeutic approaches, taking into account the diversity of disease manifestations that significantly complicate primary diagnostics and make early effective therapy impossible. In studies of the causes of ineffective asthma treatment in children, a high frequency of broncho-obstruction accompanying various pathological conditions, the complexity of differential diagnostics, as well as insufficient patient adherence to the prescribed therapy, and non-compliance with the recommended regimen are noted. Publications note the important role of psychosomatic factors in the development of asthma, as well as the link between asthma and neuroparoxysmal diseases (epilepsy). Clarifying this cause-and-effect relationship will allow us to reconsider current treatment methods as those that address the consequences rather than the cause of the disease. Addressing the underlying cause directly, using psychotherapy and anticonvulsants, will fundamentally alter the current therapeutic strategy and offer hope for a cure.

Keywords: asthma, children, adherence, neuro-immuno-endocrine regulation, psychocorrection, anticonvulsant

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Причины неуспешности в лечении бронхиальной астмы у детей. Необходимость разработки новой интегративной терапевтической программы

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АННОТАЦИЯ

Бронхиальная астма остается одним из самых частых хронических заболеваний органов дыхания у детей. Ее отличают высокий уровень заболеваемости, продолжающийся рост, инвалидизация пациентов, что определяет астму как серьезную медико-социальную проблему. Несмотря на значительные успехи в диагностике и лечении астмы за последние десятилетия, более чем у половины пациентов, получающих стандартную терапию, заболевание не находится под контролем. Необходимы тщательное изучение причин этого феномена, а также разработка новых диагностических и терапевтических направлений, с учетом разнообразия проявлений заболевания, значительно усложняющих первичную диагностику и лишающих возможности проведения ранней эффективной терапии. В работах по изучению причин неэффективного лечения астмы у детей отмечается высокая частота бронхообструкции, сопровождающей различные патологические состояния, сложность дифференциальной диагностики, а также недостаточная приверженность пациентов назначаемой терапии, несоблюдение рекомендованного режима. Многочисленными исследованиями доказана ведущая роль в формировании воспаления при астме нарушений регуляторной функции нейроиммуноэндокринной системы и, как следствие, возникновение воспаления, бронхиальной гиперреактивности. В публикациях отмечается важная роль психосоматических факторов в развитии бронхиальной астмы, а также связь астмы с нейропароксизмальными заболеваниями (эпилепсией). Уточнение причинно-следственной связи позволит пересмотреть современные методы терапии как влияющие на последствия, а не на причину болезни. Воздействие непосредственно на причину заболевания с использованием психокоррекции, антиконвульсантов позволит принципиально изменить имеющуюся терапевтическую стратегию и получить надежду на исцеление.

Ключевые слова: бронхиальная астма, дети, приверженность, нейроиммуноэндокринная регуляция, психокоррекция, антиконвульсанты

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INTRODUCTION

Bronchial asthma (BA) has been known for over 3,000 years. However, in recent decades, this pathology has become a serious medical and social problem due to the continued rapid increase in incidence and disability, despite significant advances in diagnosis and treatment using a wide range of medications for long-term symptom control. At least half of patients receiving recommended therapy experience uncontrolled asthma, which entails a high risk of exacerbations, frequent hospitalizations, and a poor quality of life. One of the main reasons for this situation is underdiagnosis.

The heterogeneity of asthma and the multifaceted nature of its symptoms pose a significant challenge for primary care physicians in establishing a diagnosis and in differentiating it from pathologies also associated with bronchial obstruction. Often, the diagnosis of asthma is replaced by less dangerous-sounding diagnoses to reassure the parents of a sick child, which subsequently leads to inappropriate therapy [12, 13]. Steroid phobia persists in the treatment of asthma, not only among parents but also among physicians: adherence to treatment recommendations is disrupted, and courses of therapy are interrupted, leading to accelerated airway remodeling and the development of complications. Lack of patient adherence to treatment and careless, technically incompetent implementation of treatment procedures are frequent contributors to failure [2, 10, 12, 13]. The primary goal in asthma therapy is to prevent severe exacerbations and severe respiratory failure, which has proven impossible with basic treatment alone [25]. This prompts the search for other approaches to asthma therapy and the development of a modern, integrative therapeutic program.

MISTAKES IN THE DIAGNOSTICS OF BRONCHIAL ASTHMA IN CHILDREN

The importance of early diagnosis of asthma is difficult to overestimate. Properly collected clinical and anamnestic data will allow the physician to correctly determine the direction of further examination to form a clinical profile of the patient.

A history of recurring episodes of wheezing (usually more than three), atopy (allergic rhinitis, food allergies, or atopic dermatitis), a strong family history, as well as severe bronchial obstruction at the onset of an acute respiratory infection, and positive dynamics with bronchodilators suggest the presence of asthma.

When collecting complaints and anamnesis, the entire range of symptoms over the past 3–4 months should be assessed, paying particular attention to those that have bothered the child over the previous two weeks.

"Wheezing" should be confirmed by a physician, as parents may misinterpret the sounds their child makes when breathing [6, 8].

When establishing a diagnosis, the response to therapy aimed at controlling symptoms should be taken into account.

Difficulties in identifying asthma in young children (the first 5 years of life) are related to the anatomical and physiological characteristics of their respiratory system, the immaturity of bronchopulmonary tissue and regulatory systems (physiological bronchial hyperreactivity), as well as the prevalence of bronchial obstruction, which accompanies a number of diseases at this age:

- congenital bronchial malformations;
- acute viral infections;
- congenital heart defects;
- tracheal foreign bodies and broncho- and thymomegaly;
- cystic fibrosis, etc.

Children are admitted to specialized clinics with alternative diagnoses, which is due to the underestimation of asthma symptoms in patients with repeated episodes of bronchial obstruction, when respiratory infections can provoke disease manifestations and have a clinically identical course. Thus, the high frequency of wheezing in children, the phenotypic "multifaceted" nature of asthma, and the inability to test pulmonary function in the first 5 years of life determine late detection, often leading to misdiagnosis, the incidence of which reaches 62% [14, 15]. Asthma often masquerades as recurrent respiratory infections in patients in the "frequently ill children" (FIC) group [14].

Problems with diagnosing asthma in children include misinterpretation of complaints, when parents mistake distant wheezing or coughing, or coughing, arising from upper respiratory tract pathology (postnasal drip syndrome) for distant wheezing [12, 13].

There is a dangerous trend in identifying asthma in children when the diagnosis is based solely on clinical history. Objective testing of the child by a physician is mandatory to confirm the diagnosis of asthma [38].

There is a common misconception in the medical community and among parents that a diagnosis cannot be made before the age of six. As a result, patients may be monitored for years with alternative diagnoses to asthma, not receiving the necessary basic therapy. This leads to inadequate symptom control, recurrent exacerbations, and hospitalizations.

Relying heavily on laboratory and functional testing methods for diagnosing asthma is inappropriate, as asthma is primarily a clinical diagnosis. Knowledge of diagnostic criteria and sound clinical judgment are fundamental to successful asthma detection [2].

Undoubtedly, laboratory methods such as ImmunoCAP, ISAC using allergy chips, determination of pulmonary function (PfE), NO concentration in exhaled air, and other procedures are extremely useful not only during the initial stages of asthma diagnosis but also during long-term patient monitoring. However, their routine use, especially by primary care physicians, often leads to misinterpretation of results. Thus, testing total IgE levels has become

almost a screening method, and elevated serum IgE levels are often considered an essential criterion for atopy, and in particular, bronchial asthma. It has been proven that approximately 30% of patients with atopy have normal total IgE levels, while bronchial asthma often exhibits monosensitization, which does not affect total IgE levels. A normal total serum IgE level does not rule out bronchial asthma and is not a diagnostic criterion [2, 28, 29].

Bronchopulmonary asthma is a heterogeneous pathology characterized by the simultaneous activation of multiple innate and adaptive immune pathways [23]. A certain difficulty in diagnosis in children is caused by manifestations of non-T2 pheno-endotypes of bronchial asthma (with neutrophilic, few-granulocyte, mixed inflammation) that are not amenable to treatment with corticosteroids and require a thorough examination with the exclusion of inflammation caused by intracellular microbiota (mycoplasmas, chlamydia) and the need to prescribe antibacterial drugs, using methods aimed at improving the condition of the respiratory tract during their remodeling [20, 26, 31].

THE IMPORTANCE OF NEUROINFLAMMATION AND NEUROPSYCHIC FACTORS IN THE DEVELOPMENT OF BRONCHIAL ASTHMA

The activity of human organs and systems, including the immune process, is regulated by the neuroendocrine system. Inflammation, as the pathophysiological basis for changes in bronchial patency in asthma, is represented by profound neuroimmune disorders underlying inflammatory processes in the bronchial mucosa and bronchospasm, and is the cause of the development of clinical symptoms. The cerebral cortex, hypothalamus, subcortical neural structures, and the autonomic nervous system play a significant role in the pathogenesis of asthma. Regulation of the neuroendocrine system in asthma is carried out through the hypothalamic-pituitary-adrenal axis (HPA), the hypothalamic-pituitary-thymus axis (HPT), and the hypothalamic-pituitary-thyroid axis. In atopic asthma, a disruption in the hypothalamic-pituitary-adrenocortical system has been demonstrated [8, 18, 34]. This disruption is primary in nature and is one of the leading pathogenetic mechanisms in the development and persistence of the chronic allergic process [22]. It contributes to the maintenance of chronic psychoemotional stress, participating not only in the development of the disease but also in the remodeling of the airways [19].

Specific brain activity preceding changes in bronchial patency has led to the conclusion that a certain type of neural activity is present in asthma. Given the importance of regulatory systems in the pathogenesis of asthma, it is advisable to distinguish its neurophenotype, which emphasizes the crucial role of dysregulation of the neuroimmunoendocrine system in asthma, the consequences of which are inflammation and broncho-obstruction [3, 39].

The psychological component of neuroinflammation has been proven to play a significant role in the development of asthma, and asthma is considered a psychosomatic disease.

Psychological stress, as well as mood disorders and anxiety states, can increase the severity of asthma symptoms. Chronic stress causes (or exacerbates) hormonal resistance, leading to the need for increased therapy [16].

Patients with asthma are characterized by high levels of anxiety, expressed in anticipation of an attack or medical care; fear, depression, fatigue, irritability, hysterical and epileptoid personality accentuation with low levels of social behavior; and self-destructive behavior, which can manifest as a predisposition to addictions (alcohol, drug, computer addiction), which creates significant difficulties in maintaining asthma control [7].

Psychosomatic risk predetermines the clinical polymorphism of neuropsychiatric disorders and their difficult-to-predict dynamics in asthma [11].

Thus, along with medication, the additional use of psychotherapy is recommended [4, 25].

The nature of asthma attacks can be epileptoid. Numerous studies have examined asthma in the context of its pathogenesis' similarities with epilepsy and other neurogenic paroxysmal and/or inflammatory diseases. Paroxysms of spasms, hypoxia, and bronchial edema are caused by pathology of the diencephalic region and reflect "autonomic epileptization". It is impossible to avoid severe exacerbations of asthma and severe respiratory failure using basic treatment alone [5, 32].

CLINICAL JUDGMENT, COMPLIANCE, AND ADHERENCE ARE IMPORTANT COMPONENTS OF THE THERAPEUTIC PROCESS

Currently, there is no cure for asthma. Asthma therapy remains suboptimal and should be aimed at maximizing quality of life while minimizing side effects and maintaining long-term control of asthma symptoms, while minimizing the risk of future asthma exacerbations and unwanted side effects of therapy [4, 29].

Airflow obstruction in asthma can partially become irreversible with conventional treatment methods alone, which defines the concept of airway remodeling. Misdiagnosis of asthma recurs when prescribing therapy.

Glucocorticosteroids are the anti-inflammatory controller therapy for asthma. Despite significant advances in asthma diagnosis and treatment over the past 30 years, it should be noted that half of patients receiving standard asthma therapy remain uncontrolled, with the risk of exacerbations and decreased quality of life remaining. The International Guidelines for the Diagnosis and Treatment of Asthma [29] note the main reasons for failure to control the disease while receiving standard therapy: lack of adherence to treatment,

technically incorrect inhalation of anti-inflammatory drugs, and failure to treat comorbid conditions [24, 30, 35].

One of the most important factors on the path to asthma control is a high level of compliance on both sides: the physician and the patient/patient's parents. The level of compliance is influenced by the type of therapy prescribed and the method of drug delivery [6, 8].

60% of patients receiving therapy do not control their asthma symptoms, and 17% only partially control them. A significant reason for failure to achieve control and an increased risk of asthma exacerbation is low adherence to basic controller therapy. Adherence to treatment with drugs for long-term asthma control is one of the key components of successful disease therapy and exacerbation prevention. Patients cite the following reasons for low adherence to maintenance therapy medications: 79% of them do not consider their condition a serious problem; 58% consider daily symptoms normal; 61% take medications only when needed; 45% are concerned about adverse reactions [1, 9].

It should be noted that patients with mild asthma are particularly precarious: 37% experience exacerbations; 18% have fatal outcomes; and 15–20% have died with mild asthma symptoms. The main causes of adverse asthma outcomes are late diagnosis, poor treatment compliance, and self-medication discontinuation. Mild asthma is prevalent among patients with poor adherence to therapy [29].

Simplifying the treatment regimen, in particular single-dose dosing, can improve patient adherence and, consequently, asthma control. Vilanterol/fluticasone furoate (VI/FF) is the first and only fixed-dose combination of an inhaled glucocorticosteroid (ICS) and a long-acting β_2-agonist (LABA) with 24-hour efficacy after a single dose [1, 35].

More recently, a triple fixed-dose combination of an inhaled corticosteroid, a long-acting β_2-agonist, and a long-acting anticholinergic has emerged as a treatment option for patients with difficult-to-treat/control asthma. Specifically, the inhaled fixed-dose combination of indacaterol acetate/glycopyrronium bromide/mometasone furoate in the Breezhaler delivery system, designed for once-daily administration, is currently under discussion [29]. Among the main causes of asthma control failure, incorrect inhalation technique should be highlighted. These factors should be considered first in patients with uncontrolled asthma symptoms [9, 29]. Adherence includes three specific components:

- acceptance of recommendations (the patient agrees to take medications/follow recommendations);
- adherence to prescriptions (the patient uses treatment as prescribed);
- persistence (the degree to which the patient follows prescribed treatment over a long period).

An adherent patient takes the medication promptly and correctly, at the full prescribed dose, maintains the recommended lifestyle and diet, and maintains psychological well-being and confidence in the success of therapy.

A non-adherent patient violates the prescribed treatment regimen, in most cases without realizing the potential consequences. Non-adherence to therapy is directly associated with an increased frequency of exacerbations and hospitalizations, the use of oral glucocorticosteroids, unscheduled asthma-related doctor visits, and a reduced quality of life. Many patients do not even begin using asthma controller medications after their doctor's prescription [21, 37], or discontinue their controller medications prematurely, despite the risk of exacerbation [24].

Factors that reduce patient adherence to asthma treatment include complex dosing regimens, side effects and delayed effects of medications, their cost, and the presence of concomitant diseases [9].

The following types of non-complience are distinguished: unintentional (forgetfulness, fear of high costs, lack of understanding) and intentional (prejudice, fear of side effects, cultural issues, financial insolvency) ones.

It is difficult to predict poor adherence because there is no typical non-compliant patient, and low adherence is usually due to a variety of reasons, including patient characteristics and external factors unrelated to the patient [33].

The best ways to identify low compliance with treatment are patient observation, disease control assessment, well-formulated questions about the use of basic asthma therapy, and checking the date of prescription, expiration date, and dose counter. Informing and educating patients, partnering with them in treating asthma, and a simple treatment regimen that involves a single dose of medication to control symptoms (once a day) or a single inhaler regimen are key to optimal adherence to treatment [1].

It should be noted that most patients with asthma prefer to take medication once a day [1, 36].

Clinical remission of severe asthma is partly possible through targeting biomechanisms, but it is impossible to assess the effect of biotherapy, as biomarkers do not reflect the complexity of inflammatory endotypes and are insufficient for drug selection [27].

BRONCHIAL ASTHMA NEUROPHENOTYPE AND THE CREATION OF AN INTEGRATIVE THERAPEUTIC PROGRAM

It is impossible to achieve complete disease control using only basic therapy. Even when remission is achieved, treatment is continued throughout the patient's life, often with increased medication volumes. The adequacy of this approach is questionable, although its necessity is clear [3, 8, 11, 17, 36]. Therefore, to achieve high treatment efficacy, it is necessary to supplement accepted standards of asthma therapy.

Until now, asthma patients have been treated in two main ways: by targeting the factors that trigger the allergic reaction and the various links in the pathogenesis

of the allergic reaction; and by targeting peripheral receptors located in the bronchial wall. Both of these approaches essentially involve targeting trigger factors. Based on the results of studies demonstrating the neuroparoxysmal mechanism of bronchospasm in asthma, a third therapeutic approach is recommended: targeting the activity of the generator neurogenic paroxysmal mechanism of asthma attacks using anticonvulsants. This leads to their prevention and opens new horizons in asthma treatment. M. Lomia et al. [32] achieved compelling positive results in the treatment of patients with AD using anticonvulsant therapy.

Given the significant role of psychological factors in the development of AD, an important approach to its treatment is the introduction of psychological correction methods that alter the pattern of brain activity toward normalizing the interactions between brain regions using various techniques and standardized therapeutic programs [5, 25].

American scientists have proposed using mindfulness meditation programs, or mindfulness therapy (self-regulation of attention), with the perception of the external and internal world as it is: without criticism, evaluation, or condemnation. This technique allows for the integration of neuroscience and pharmacotherapy in the treatment of AD [25].

Thus, to improve the effectiveness of AD treatment in patients, it is necessary to consider the use of anticonvulsants and psychological correction methods in addition to the medications currently being taken [5, 11, 25, 32].

Monitoring children with asthma requires a multidisciplinary team of specialists (including a psychologist, psychotherapist, allergist, and pediatrician). This will help identify new therapeutic strategies, periconceptual prevention of exacerbations, and, possibly, pave the way to a cure for asthma.

As already noted, given the importance of regulatory systems in the pathogenesis of asthma, it is advisable to identify its neurophenotype, which will allow for an objective assessment of the crucial role played by the underlying cause of asthma pathology — dysregulation of the neuroimmunoendocrine system, which results in inflammation and bronchoconstriction.

The heterogeneity of asthma and the antitrigger approach to treatment are the basis for unresolved therapeutic issues. The lack of clarity in understanding the cause-and-effect relationship of the mechanism of asthma development gives rise to numerous descriptive clinical variants (pheno-endotypes), which do not address the underlying problem. Without a radical intervention to address the underlying cause of asthma, the possibility of recovery is excluded.

CONCLUSION

A number of mistakes are made in the diagnosis of asthma in children:

- failure to differentiate asthma from bronchial obstruction in other diseases in young children;
- misinterpretation of complaints (such as distant wheezing);
- replacing the diagnosis of asthma with a less serious one, followed by inadequate therapy;
- overestimating the importance of additional examination data and misinterpreting them.

The following errors are made in the treatment of patients with asthma:

- underestimating the significance of relatively mild asthma and inappropriate therapy;
- poor patient adherence to prescribed treatment;
- erroneously focusing the therapeutic vector on the consequence rather than the cause of the disease, excluding the possibility of recovery;
- underestimating the significance of neuroinflammation in asthma, which makes it advisable to identify the neurophenotype of asthma with the targeted use of anticonvulsants and psychological correction in treatment, along with accepted drug therapy.

Thus, **an integrative diagnostic program for asthma** in children, developed based on the results of numerous studies, includes the following:

- dissemination of in-depth knowledge of modern asthma diagnostic criteria among practicing physicians using innovative technologies;
- careful compilation of a clinical profile of the patient;
- identification of comorbid pathology (allergic pathology);
- clearly defining the child's examination vector to clarify the asthma phenotype and endotype for subsequent phenotype-specific therapy;
- careful monitoring of the patient's condition, determining their degree of adherence to treatment;
- further research to establish a causal relationship in the development of asthma and possible changes in the therapeutic vector.

The proposed steps in adjusting the programmatic diagnostic and therapeutic approach to asthma will help bring us closer to solving one of the most important medical problems — the cure of asthma.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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