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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

RISK FACTORS AND CLINICAL-EPIDEMIOLOGICAL FEATURES OF ATOPIC DERMATITIS AMONG CHILDREN IN BAKU CITY

Speciality: 3222.01- Skin and venereal diseases

Field of science: Medicine

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BAKU – 2022

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GENERAL CHARACTERISTICS OF THE DISSERTATION WORK

The actuality of the dissertation work. The atopic dermatitis occupies the leading place in the structure of skin and subcutaneous tissue diseasesin children. Atopic dermatitis (AtD) is considered as one of the most common skin diseases, is characterized by increasing recurrence of the disease and responds to therapy poorly. AtD is a chronic allergic immune-dependent inflammatory process, develops in individuals with a genetic predisposition to atopy and is a disease with symptoms of secondary immunodeficiency, including age-related clinical signs, recurrent course, and exudative or lichenoid rash, elevated serum IgE levels, and hypersensitivity to specific (allergenic) and nonspecific irritants, sometimes leading to disability in children. Cases of disability in patients with AtD reaches 8%.[1;2;3;4]

AtD belongs to the group of allegro-dermatoses and is seen in overall 20% of all patients suffering from allergic diseases. As it is known, AtD occurs in different age groups – from early age to old age, but often debuts in the first years of a child's life.[5;6;7;8;9;10]

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This diseases worsens the life quality of patients with AtD and their family members. That's why, studying the prevalence, features of manifestations of AtD and development of the main directions of medical-preventive measures is one of the important problems of modern medicine.

From the epidemiological point of view 3.5% of people in the world face AtD problems. Cases of AtD among children in developed countries changes between 4% and 37%, but the prevalence rate among old people is low and it changes between 0.2% and 2% depending on the geographical region.[11;12;13;14] All these facts makes AtD big social problem. Immunological changes play a leading role in the pathogenesis of AtD. The disease is characterized by disregulation of the T cell ring of cellular immunity

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and by the hypersensitivity to many immune and non-immune stimulants. In recent years in the medical literature more attention has been paid to epicutane sensitization and the cytokine component of the allergic inflammatory process (including residual inflamematory activity in the skin).[15;16;17] The immunopathogenesis of atopic dermatitis traditionally is considered as a violation of the balance of Th1 / Th2 and the profiles of their cytokines. However, different cytokines are involved in the pathogenesis of AtD and they are produced by other regulatory cells (Treg, Tr1, Th17, Th22, etc.), not only by antagonistic subpopulations of Th1 and Th2 lymphocytes. But in recent years the notion of atopy is thus substantiated as following: atopy is a phenomenon, in development of which as both immune, IgE-conditioned, and numerous non-immune mechanisms are involved. From the point of view of the prognoses of the disease the great attention is being paid to skin remodelling - reversible morpho-functional reconstruction processes dependent on the activity of various cytokines.[18;19;20] One of the methods of complex approach to the assessment of the child's condition is the definition of quality of life (LQ) so that, traditional examination methods create a

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one-sided view of the disease. LQ is a broad concept and covers medical, psychological and social aspects. Definition of parameters of LQ is conducted on both healthy and sick children and in this case, the course of AtD has a significant impact on quality of life.

Assessment of LQ is the second method of determining the effectiveness of treatment (after the Kaplan-Mayer method - for survival). Assessment of LQ allows a more sensitive and complete studying of the child's health and the effectiveness of treatment.[21;22;23;24]

AtD is of great interest among specialists of different profiles - paediatricians, allergists, dermatologists. This approves the fact that the level of morbidity in children is constantly increasing in the first months of life – the period of the formation of the intestinal microbiota and the immune system, i.e. during the period when the physiology of the gastrointestinal tract (GIT) and metabolism is established and it determines the health of children in the future. Prevention of the disease is the most important issue in solution of the problem of AtD. Because of this, identification of risk factors, which have real importance in the prognosis of the disease and allows them to plan effective preventive measures, plays a special role in the prognosis of the disease.

The importance and relevance of the study of the epidemiology of AtD in children, conducting their analysis and comparing them with official statistics according to the international standardized protocol, defined the goals and objectives of the given study and the

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level of prevalence of symptoms of AtD in children was studied during conducting of research works.

The object and subject of the study: 112 children aged between 1 and 15 years with atopic dermatitis were examined during 2014-2019 - while fulfilling the goals in accordance with clinical and laboratory criteria. These children form the main group of patients with atopic dermatitis; additionally 55 practically healthy children, with unchanged allergic reactivity and without chronic infection in the body, have been involved to the study. Significant differences by age and gender of children in main and control groups were not statistically important. The children in the main group were divided into 2 subgroups: 64 childrenare - children with AtD complicated by secondary infection (group 1), 48 childrenare - children with AtD not complicated by secondary infection (group 2).

The purpose of the study: To study the clinical and epidemiological features of this disease, which was diagnosed based on the identification of leading risk factors for the development of AtD during screening examinations in children.

Objectives of the study:

1. To assess the prevalence of among children aged between 1 and 15 years in Baku city;
2. To reveal the characteristic clinical and epidemiological features of the disease based on clinical-laboratory and functional examinations of children with atopic dermatitis;
3. To identify the leading risk factors and risk groups for the development of ATD in children. To specify the role of risk factors for formation of immune and non-immune mechanisms of the pathogenesis of AtD;
4. To determine the nature of changes in immune status and parameters f life quality during AtD in children;
5. To develop prognostic algorithms necessary for screening examinations of AtD.

Methods of the study: Instrumental, clinical, epidemiological, immunological, bacteriological and statistical examination methods have been used in research work. Formation of diagnosis was conducted according International Classification of Diseases 10th

Review accepted on 01.01.99 by the 43rd World Health Assembly. Date of onset of the disease, severity of pathological changes, the degree of spread of the process, the frequency of exacerbations and their duration, the effectiveness of previous treatment have been assessed. Information about results of epidemiological studies implemented by means of international program ISAAC have been presented.

Main provisions of the dissertation to be defended:

1. Development of new approaches to the diagnosis of ATD in children taking into consideration the pathogenetic aspects as leading risk factors aimed at eliminating the identified violations.

2. Timely diagnostics of AtD in children allows to optimize treatment measures in patients with this pathology.

3. The algorithm for determining the prognosis of AtD, developed based on the identified risk factors, allows to optimize the prevention of this disease.

Scientific novelty of the study:

1. AtD prevalence levels by age and gender have been studied for the first time in Baku city, obtained statistical data have been studied, clinical-laboratory and functional examinations of patients were conducted.

2. The nature of immune status in children with AtD have been studied, the role of subpolation of suppressor T-lymphocytes in immune pathogenesis of AtD have been detected. Moderate changes in all parameters and statistically significant changes in T-helpers and T-active CD3 +, CD4 +, CD25 + cells were detected while re-measurement of subpopulations (after treatment) in group of children with complicated disease.

3. Risk factors of prevalence of AtD among children in Baku city have been identified and divided into two groups (Risk factors that lead to the development of AtD and contribute to the exacerbation and progression of the disease after confirmation of AtD diagnosis).

4. A set of questions on quality of life indicator, including medical, psychological, social aspects was developed by adapting to children with AtD. Assessment of life quality allows to assess the

child's health condition and the effectiveness of treatment more sensitively.The overall low life quality indicator of children with AtD was 13.7 points even in remission period.

5. The diagnostic algorithm for period of AtD have been developed and it includes careful collection of anamnesis of the current disease, sampling for complex examinations, improvement of their diagnosis, guidelines for different treatment methods and development of new approaches to the treatment of AtD in children.

Practical and theoretical significance of the study:

According to the obtained informationthere is an idea that risk factors, creating immunological and non-immune parts of AtD, must coexist. These ideas expand capacities of treatment and prevention of AtD. Development of algorithm allowing to determine the sequence of prognostic steps and prophylactic effects to neutralize the risk of AtD as experience is very important. Implementing of awareness-raising activities on perinatal and postnatal risk factors with women with allergic diseases during pregnancy is considered as important issue. Taking into consideration the fact that the saprophytic flora of skin, in treatment resistive forms of AtD, increases and aggravates the course of the disease, local appointment of antibacterial and antifungal drugs, depending on age of a child and severity of the disease, is important.

Application of results of the study:

Achieved results of the research work are being used in the diagnosis and treatment of relevant patients in the polyclinic department of the Children's Dermatovenerologic Dispensary No. 3 and the Republican Dermatovenereological Dispensary. Besides it, separate provisions of the dissertation y were included into the curriculum on epidemiology of At the Department of Epidemiology of Azerbaijan Medical University.

Approbation of the dissertation: Separate provisions of the dissertation have been reported at the Scientific-Practical Conference on topical problems of medicine dedicated to the 100th anniversary of the Azerbaijan Democratic Republic (Baku, Azerbaijan, September 2018), at the International Scientific-Practical Conference dedicated to the 100th the establishment of the

Department of Human Anatomy and Medical Terminology of the Azerbaijan Medical University (Baku, Azerbaijan, 2019), at the International Scientific-Practical Conference on topic "XXVII - XXVIII modern medicine: new approaches and current research" (Russia, Moscow, October 2019), at the Scientific-Practical Conference dedicated to the 90th anniversary of the establishment of the Azerbaijan Medical University (Baku, Azerbaijan, December 2020), at the International Scientific-Practical Conference dedicated to the 85th anniversary of Professor M. Davatdarova (Baku, Azerbaijan, September 2020), at the International Scientific-Practical Conference on "Achievements of modern medicine in the field of studying the epidemiology of infectious diseases" (Uzbekistan, Tashkent, June 2021), the International Scientific-Practical Conference on "Science and Education" (Russia, Tambov, May 2021).

Materials of the dissertation were reported and discussed on the meeting of the Department of Dermatovenerology of Azerbaijan Medical University (28.12.2021 year, protocol №4), at the scientific seminar under the Dissertation Council of the Azerbaijan State Advanced Training Institute for Docters named after A.Aliyev (05.07.2022 year, protocol №7) .

Publications: Texts of dissertation materials are given on 9 journal articles, 2 of them on international journals, and on 7 conference materials.

The structure of the dissertation:

The dissertation is consisting of introduction, literature review, research materials and methods, 5 chapters of special study, conclusion, results, practical recommendations and list of bibliography.

The total volume of the dissertation by symbols is 230748 symbols: introduction - 12204 symbols, Chapter I - 57614 symbols, Chapter II- 18138 symbols, Chapter III - 30333 symbols, Chapter IV- 28880 symbols, Chapter V - 47988 symbols, conclusion - 29641 symbols, results – 4408 symbols, practical recommendations - 1542 symbols.

The dissertation is presented in form of text consisting of 169 pages printed in computer, includes 19 tables and 28 figures. The list

of bibliography consisting of 204 sources, 86 of them are in Russian and 118 – are in other languages.

CONTENT OF THE DISSERTATION

Materials and methods: The dissertation work was conducted within the scientific program of the Department of Dermatovenereology of AMU during 2014–2019 years. The study was carried out at the Department of Dermatology of AMU and Children's Dermatovenerologic Dispensary No. 3, which is the basis of AMU, using the prospective method.

For implementation of the purpose of the dissertation work in accordance with clinical-laboratory criteria 112 children with atopic dermatitis aged between 1-15 years have been examined during 2014-2019 years within the frames of the given study. These children consisted the main group of patients with AtD; besides it 55 practically healthy children with unaltered allergic reactivity and no foci of chronic infection in the body have been involved to the study as members of the control group. The differences by age and gender in examination groups were not statistically significant. Children in the main group were divided into two sub-groups: 64 of them were children with AtD complicated by secondary infection (sub-group1), 48 - were children without AtD complicated by secondary infection (sub-group 2).

Criteria for including to the study were: patients aged between 1-15 years with diagnosed AtD, possibility of dynamic observation of patients, consent of parents to participate in the study.

Criteria for excluding from the study: the patient's age is over 15 and up to 1 year, the patients with acute infectious processes (ARVI, rhinitis, pharyngitis, etc.) or concomitant allergic diseases (bronchial asthma, allergic rhinitis, pollinosis) at the time of observation were not included to the stud, parents' refusal to participate in the study.

The main complaints of patients were studied, the anamnesis of the current disease, allergy anamnesis, life history were diligently collected, the patient was objectively examined, the external skin was

examined for determining of the presence of fungal diseases in the body while examination of patients suffering from AtD. Formation of the diagnosis was performed according to the International Classification of Diseases 10th Review adopted by the 43rd World Health Assembly on 01.01.99. The date of the onset of the disease, the severity of pathological changes, the prevalence rate of the process, the frequency of exacerbations and their duration, the effectiveness of previous treatment were assessed. Data of epidemiological research work conducted by means of the international program ISAAC showed that, the prevalence rate of AtD among children in Baku city from 2014 to 2019 year -was 12.04±1.8%. All laboratory examinations of 112 patients with AtD were performed in dynamics before and after treatment. The control group was consist of 55 healthy children (32 girls (58.2±6.7%) and 23 boys (41.8±6.7%)). 76 of examined patients in the main group were girls (67.9±4.4%) and 36 were boys (32.1±4.7%). Division of examined children in the main group by age and gender is given in Table 1.

Table 1

Division of children with AtD by age and gender

Age	1-5 years		6- 10 years		11 -15 years		Total	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Girls (n=76)	33	43,4± 5,7	32	42,1± 5,6	11	14,5± 4,1	76	67,9 ±4,4
Boys (n=36)	13	36,1± 8,0	16	44,4± 8,3	7	19,4± 6,5	36	32,1 ±4,7
Total	46	41,1± 4,6	48	42,9± 4,7	18	16,1± 3,5	112	100

112 children in the main group were divided into 2 subgroups: 64 of them had AtD aggravated by secondary infection and consisted the 1st subgroup, 48 children consisted the 2nd subgroup with AtD not aggravated by secondary infection. In subgroups of patients, with AtD aggravated and not aggravated by secondary infection, children

were also divided by gender and the majority of patients are boys: 24 patients (66.7 ± 7.8%) in the 1st sub-group and 12 patients (43.4 ± 7.8%) in the 2nd subgroup. Share of girls was respectively 40 patients (52.6±5.7%) in the 1st sub-group, and 36 patients (47.4±5.7%) in the 2nd sub-group. The objective severity of the disease was assessed as following: mild - in 5 patients (4.5 ± 1.9%; p <0.001), moderate - in 48 patients (42.9 ± 4.7%), severe - in 59 patients (52.6 ± 4.9) %; p <0.001). Patients were distributed by severity as following (Table 2).

Table 2

Division of children with AtD by severity of disease

Age	Severity						Total	
	Mild (n=5)		Moderate (n=48)		Severe (n=59)			
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
1st group- aggra- vated by secon- dary infection (n=64)	2	3,2	17	26,6± 6,4	45	70,2± 5,9	64	57,1± 4,7
2nd group - not aggra- vated by secon- dary infection (n=48)	3	6,3	31	64,6± 6,4	14	29,1± 5,9	48	42,9± 4,7
Total	5	4,5± 1,9	48	42,9± 4,7	59	52,6± 4,9	112	100

Division of children with diagnosed AtD to groups as aggravated and not aggravated by secondary infection showed that, the highest number of patients in group 1 was registered as severe

patients (45 patients, 70.2 ± 5.9%), 17 patients (26.6 ± 6.4%) were registered as moderate, and 2 patients (3.2%)- as mild. Most of patients in the 2nd group of patients with AtD not aggravated by secondary infection were moderate patients (31 patients, 64.6±6.4%), severe patients - 14 (29.1 ± 5.9%), mild patients - 3 (6.3%). Also, in all patients in each group suffering from AtD, depending on the form of the disease erythematous-squamous and erythematous-squamous with lichenification were observed. AtD manifested in 47 (41.9± 4.7%) children with erythematosus-squamous form and in 65 children (58.1±4.7%) with erythematosus-squamous form with lichenification.

Due to the duration of illness, division of patients as patients with AtD aggravated and not aggravated by secondary infection showed that, the number of patients suffering from AtD more than for 2 years in the 1st group was 5 patients (7.8±3.3%), and 19 patients in the 2nd group (39.5±7.1). Morbidity rate among children aged from 2 to 4 years in groups was respectively: 43 patients (67,2±5,9%) in the 1st group, 26 patients (54.2±7.2%) in the 2nd group.

The number of those suffering from AtD more than 4 years by groups was: 16 patients (25.0±5.4%) – in the 1st group, 3 patients (6.3±3.6%) in the 2nd group. Division of children by the duration of illness was as following: less than 2 years - 24 patients (21.4±3.9%), from 2 to 4 years - 69 patients (61.6±4.6%), more than 4 years – 19 patients (17.0±3.5%). The localized form of the disease was seen in 18 (16.1±3.5%) patients, the common form in 68 patients (60.7±4.6%) and diffuse form - in 26 (23.2±3.9%) patients. In 100% cases the localized form of AtD was observed among patients with mild form the disease. The localized form of AtD in patients with moderate form of disease was characteristic for 13 cases (27.1±7.4%) and common form – for 35 cases (72.9±6.4%). The common form of disease was characteristic for 33 children (55.9±6.4%) and the diffuse form – for 26 children (44,1±6,4%) with severe AtD.

The frequency of periodic applications of patients with AtD due to exacerbation of the disease i 2-4 times a year, mainly 2 times a year (42 patients, 37.6 ± 4.6%). Together with exacerbation of the

disease in patients with AtD in spring (from March till May) seasonal dynamics of clinical manifestations is characteristic and It is determined by the nature of the flowering of various plants that are a source of allergens and the body's immunosuppressive state in the spring. In 106 (94.6±2.1%) patients with AtD concomitant diseases have been found. These diseases are mainly represented by different types: dysbacteriosis - 73 patients (65.2 ± 4.5%), bronchial asthma - 38 patients (33.9±4.5%), allergic rhinitis - 32 patients (28.6 ± 4.3%), pollinosis - 25 patients (22.3±3.9%), food allergies - 18 patients (16.1±3.4%), otitis - 15 patients (13.4±3.3%), sinusitis - 12 patients (10, 7±2.9%), Quincke's edema - 8 patients (7.1±2.5%). Depending on the clinical course, the following types of ATD were distinguished: primary - 18 patients (16.1±3.4%), exacerbation - 23 patients (20.5±3.8%), chronic - 38 patients (33, 9 ± 4.5%), remission - 21 patients (18.8±3.7%), clinical recovery - 12 patients (10.7± 2.9%).

Exacerbation of ATD occurred mainly: in 67.9±4.4% (76 patients) of cases with gastrointestinal dysfunction, in 52.6±4.9% (79 patients) of emotional factors, in 42.9±4.7% (48 patients) of cases respiratory infections and in 21.4±3.9% (24 patients) of cases tooth extraction. Patients with atopic dermatitis have been exposed to infectious skin diseases such as: 58.1±4.7% (65 patients) - pyoderma, 61.6±4.6% (69 patients) - viral and 41.9±4.7% (47 patients) - fungal infections.

The patients had the following complaints: pruritus - 112 children (100%), sleep disorders - 59 people (52.7±4.7%), papular rash - 72 people (69.7±4.4%), pustular rash - 34 people (30,4± 4.4%), dry skin - 112 children (100%). Papular rash is typical was observed on mil-wrist flexion, elbow and knee joints, arm area, and manifested by localization on the medial surface of the thigh, itching in the areas of skin lichenization, red or white dermographism in undamaged areas of the skin.

The followings were observed in ultrasound examination of the abdominal organs during the acute phase of the disease: reactive changes in liver tissue in 32.1±4.7% of children (36 patients), 24.1± 3.9% (24 patients) - signs of biliary dysfunction of hypotonic type, in

16.1±3.5% of cases (18 patients) signs of diffuse changes in the tissue of the pancreas were visualized. Analysis of the obtained questionnaires showed that, 14.3±3.3% of children have previously complained of itchy rash lasting at least 6 months. There were more girls among them than boys (15.8±4.2% and 11.1±5.4%, respectti-vely, $p < 0.001$). 51.8±4.7% of children indicated localization of skin rash along with itching in typical parts of the body (elbow and knee bends, ankles, under the buttocks, around the neck, eyes, ears) and the number of girls with rash with characteristic localization was relatively more than boys (61.8±5.6% and 30.6±7.7%, respectively, $p < 0.05$). 25.9±4.1% of children reported the first occurrence of pruritus before the age of 2, numbers of girls and boys was nearly same (respectively 26.3±5.1% and 25.0±7.2%). 39.3±4.6% of chil-dren aged 2-4 years and 34.8±4.5% children aged 5 ≥ said about itchy rash. During the last years in 57.2±4.7% children the itchy rash was not completely gone.

The conducted examinations discovered that, virtually all of the interleukins and chemokines we have studied can be involved in circulation, both in children with AtD and in children without signs of allergic inflammation. The anti-inflammatory interlayer was found in the serum of all children in the TGF-β1 comparison group and 97.3% of children with AtD. Although the incidence of TGF-β1 is high among children of the main group, a significant decrease of its level in serum in comparison with children without atopy is characteristic ($p=0.0034$). IL-22 occupies the third place due to frequency of occurring in serum of children with AtD and it is found in 54.48% of cases (in contrast to the comparison group - 40.8%). Its average value in the serum of children of the main group was almost 5 times higher than children of the control group ($p=0.03$). In this case, the same feature - a wide range of changes in the performance of this interlayer is observed in children with AtD. Examination of serum cytokine profile of patients with AtD revealed that IL-4, IL-5, IL-13 (their role in the development of allergic diseases is widely accepted)were found only in 23.58%, 33.68%, 36.98% of patients, and in the comparison group, respectively, in 35.98%, 100%, 18.73% cases. An increase in IL-4 and a decrease in IFN-g are observed in

the remission period of AtD. It is also characteristic for acute period of disease and shows the atopic character of the pathology. In comparison with healthy parts of the skin an increase in the amount of IL-10 in lichenification centers is noted and it shows that this cytokine plays an important role in skin remodelling processes in patients with AtD.

One of the mechanisms of formation of AtD is imbalance in the complex of effector and suppressor mechanisms aimed at maintaining the stability of the internal environment. We detected CD4 + CD25 + Lymphocytes (marked as "active") and CD4 + CD25 + (high) -Tymphocytes (marked as T-regulator (T-reg)) in out study. During the study statistically significant differences in the percentage of T-active cells in remission were found in blood of 8.6 of healthy children 8,3 (μL) and 2.60 (μL) children with AtD ($p<0.001$).While analysing of correlation dependence in children with remission of AtD we found that the positive correlation of T-active lymphocytes with T-reg sells was $r=0.757$ and negative correlation with T-total sells was $r= - 0.523$ - ($p<0,001$). In healthy children no relationship between CD4 + CD25 + and other lymphocyte groups was found.

Statistically significant differences in the amount of T-reg sells were found in the exacerbation phase in groups of healthy children and in groups pf children with AtD, as well as in remission and exacerbation phases in groups with AtD. Depending on the level of expression CD25 + hi in a group of healthy children was 0.42 (μL), In the group of children with exacerbation of AtD was 1.60 (μL) and was 0.05 (μL) in the remission group of AtD. The calculation was based on the percentage of CD3 + CD4 + immunophenotype from the total number of cells. Sharper distribution of indicators was observed in the group with exacerbation of AtD.

Risk factors for the development of AtD are divided into two groups according the results of conducted research works: pre- and perinatal risk factors leading to the development of the disease and Postnatal risk factors that lead to exacerbation and progression of the disease after the diagnosis of AtD. It became clear that the share of perinatal risk factors in the pathology of pregnancy and childbirth is high as a result of comparative assessment of the possibility of

influencing the development of AtD. If we will observe the perinatal risk factors in a differentiated way, it becomes clear that, in comparison of children in the 1st and 2nd groups 60.9±6.1% (39 children) were born on time, and 81.2± 4.8% (52 children) were born by caesarean section in the group of children with secondary infection, these indicators in the group of children without with secondary infection were, respectively, 85.4±5.1%, $p<0.01$ (41 children) and 62.5±7.0%, $p<0.05$ (30 children). It also should be noticed that, among newborns in the 2nd group the neonatal resuscitation is used more frequently. It also was approved by the fact that the first krying cases of newborn immediately after birth was significantly lower (92.2±3.4%) in group 1 children than in group 2 (91.7±3.9%; $p\leq0.05$).

Conducting comparative characterization among the postnatal factors, seen in children with AtD, we have identified the factors that we can combine. They are intestinal, infectious and lymphoproliferative syndromes. Intestinal syndrome in children manifest by intestinal dysbiosis, chronic MBY diseases, parasitosis and intestinal infections and their comparative characterization are attracted in the following information: The incidence of intestinal dysbacteriosis is approximately the same in both groups of children and no statistically significant differences were observed during the comparative characterization of this factor. Examinations showed that, parasitic invasions represented by helminthiasis and protozoal infections are significantly higher in children in group 1 (45.3±6.2%) than in children in group 1 (33.3±6.8%, $p\leq0.05$). %). Children in group 1 also suffer from chronic diseases of the gastrointestinal tract. In a group of children complicated by a secondary infection, number of children with breastfeeding for up to 1 year was 18.6±4.9% (12 children), those with adenoiditis 12.5±4.6% (8 children), this indicator was respectively 91.7±3.9%, $p<0.001$ (44 children) and 29.2±6.5%, $p<0.05$ (14 children) in children not complicated by secondary infection.

The next syndrome in children with AtD, which is clearly visible from infectious factors are common respiratory viral infections and herpes simplex viruses in children with AtD. The

frequency of respiratory viral infections in both examination groups was 70.3±5.6% and 72.9±6.4%, respectively by groups. No statistical accuracy was found on this risk factor during the comparative analysis. Frequency of viral infections in children in both groups also was similar. Although there are no statistically significant differences, infectious syndrome plays an important role as a risk factor for the development of AtD, thus, high frequency in children with AtD in both examination groups is observed.

During the comparative characterizing of prenatal risk factors it was found that, inthe 2nd group of children the specific share of aggravated genealogical anamnesis in pregnant women (68.7±6.7%) is higher than in mothers of children in group 1 suffering from AtD (25.0±5.2%; $p \leq 0.05$). The frequency of some factors, such as chronic diseases of the pregnant women, is also higher in women in the 1st group (32.8±5.8%) than in women fron the group 2 (14.5±5.2%). Chronic stress was significantly higher in women in group 2 (8.3%) than in women in group 1 (3.2%). At the same time, the professional harms in women in group 2 (8.3%) are much lower than in women in group 1 (18.6±4.9%; $p \leq 0.05$). Complicated genealogical history of atopy, which is a prenatal risk factor for the development of AtD in children, remains an uncontrollable factor and it is practically impossible to influence it. The fact that pollinosis has a great influence on the characterization of genealogical anamnesis also attracts great attention.

Results of comparative characterizing of prenatal and perinatal risk factors of of children with AtD in Baku city is attracted in Table 3.

For better identifying of the risk factors of AtD by conducting the scrinning examinations an algorithm for preventive and curative measures in children with AtD has been developed. It is necessary to focus on risk syndromes that characterize the neurological and immunological component of the pathogenesis of AtD during the screening examinations for identifying of development risk factors of AtD. For being more confident that there is a real risk of developing AtD it is advisable to use of the proposed algorithm and observation

Table 3

The frequency of pre- and perinatal risk factors in groups of children with atopic dermatitis in Baku city

Risk factors	Comparative groups				t	P
	Group 1 (n=64)		Group 2 (n=48)			
	Abs	%	Abs	%		
Complicated genealogical anamnesis of children (allergic diseases of parents)	16	25,0 ±5,2	33	68,7 ±6,7	5,15	<0,001
Professional harms of mother	12	18,6 ±3,9	4	8,3± 2,9	2,12	>0,05
Chronic diseases in pregnant woman	21	32,8 ±5,8	7	14,5 ±5,2	2,35	<0,05
Chronic stress in pregnant woman	2	3,2± 1,2	4	8,3± 1,9	2,27	>0,05
Pathology of pregnancy	48	75,0 ±5,4	21	43,8 ±7,1	3,49	<0,001
Complications at birth	26	40,7 ±6,1	16	33,3 ±6,8	0,81	>0,05
Intrauterine or postpartum CNS damage in children	29	45,3 ±6,2	12	25,0 ±6,3	2,29	<0,05
Pathology of the neonatal period	45	70,3 ±5,6	14	29,2 ±6,5	7,34	<0,001
Duration of the first breastfeeding (1st hour)	8	12, 5±4, 6	29	60,4 ±7,0	5,71	<0,001
The duration of breastfeeding is up to 1 year	14	21,9 ±5,2	38	79,2 ±5,8	7,35	<0,001
On time birth	39	60,9 ±6,1	41	85,4 ±5,1	3,08	<0,01

Table 3 (continuation)

New-born cried immediately after birth	59	92,2 ±3,4	44	91,7 ±3,9	0,09	>0,05
Caesarean section	52	81,2 ±4,8	30	62,5 ±7,0	2,20	<0,05

by a team of specialists with the participation of an immunologist and a neurologist when relevant risk factors are identified. It is advisable to include in the plan of prevention and treatment measures means that affect the macrophage-phagocytosis ring of the immune system in case of AtD in children.

Comparison of questionnaires on the assessment of the quality of life of parents and their children showed that only in 1/3 of the cases the data overlap, the index of life quality in 65.9±1.1% of parents was lower than in their children and it indicates that children and their parents need psychotherapeutic help in families whose children have AtD.

Various microorganisms have settled on skin of children suffering from AtD, in the main group their number was much higher than that of the children in the control group. Infectious diseases of the skin in patients with atopic dermatitis are: 58.1±4.7% of cases (65 patients) to pyoderma, 61.6±4.6% (69 patients) of viral and 41.9 ±4.7% (47 patients) of fungal infections this feature attracts the immunodeficiency condition which is characteristic for patients with AtD. But it is more important from the clinical point of view. Regardless of the severity of the process, the patients with atopic dermatitis are tend to become infected by viral infection in 61.6± 4.6% of cases, herpes simplex virus in 33.9±4.5% of cases. "Kaposi's herpes-shaped eczema" developed in 3 cases (6.4±3.6%) and this reflects a lack of cellular immunity. It became clear that, in 98 patients with AtD (87.5±3.1% of cases) staphylococcal gold contamination of the skin has been recorded, and its density was more pronounced at the sites of localization of lesions. Staphylococcus epidermidis (77.6±3.9%) is also important among bacterial factors. In case of AtD bacterial infections of the skin in children

occur both without the manifestation of clinical signs of infection (61.6±4.6%) and in the form of pyoderma (38.4±4.6%): superficial (77.6±3.9%) and deep (22.4±3.9%). The results of the mycological examination showed that, 32.1% - yeast fungi, 33.5% - dermatophytes, 22.4% - mold fungi and 12.0% - associations of several fungi were planted in 25.0±4.1% of children with AtD and fungal colonization of the skin. In structure of examined children with AtD the specific gravity of patients with non-staphylococcal flora of bacterial etiology and their colonization with fungi was negligible and it covered only 18.0% of all patients.

Appointment weak (1% hydrocortisone, 0.05% alclomethasone dipropionate) or mild (0.1% hydrocortisone -17-butyrate) topical glucocorticosteroids (GCS) twice daily, as well as moisturezers and of emollients is sufficient for patients with mild signs of AtD (SCORAD up to 20 points) when the process is limited or disseminated. These liniments are applied to the damaged areas of the skin 2-3 times a day.The various therapeutic agents are used externally depending on the clinical picture of AtD and the location of the lesions of the skin. The duration of therapy with topical GCS is determined individually, but should be no longer than 14 days.

Topical inhibitor of calcineuria - 1% pimecrolimus cream may be prescribed to patients in case of limited process or disseminated rash with low or moderate inflammatory activity (SCORAD up to 20 points), in rashes of any localization, including on the skin of the face, neck, wrinkles. It is applied twice a day to the area where the clinical signs of AtD are noticeable. Duration of the main treatment course is 2-4 weeks. Application of 1% pimecrolimus does not lead to the development of side effects typical of typical GCS, as well as the development of pyogenic and viral superinfections. Application of 1% pimecrolimus cream also may be useful in when other drugs are ineffective at the prescribed dose and time parameters, as well as in sensitive areas in case of rash in case of intolerance to topical GCS In order to prevent the risk of developing additional symptoms that are characteristic of GCS. Inncase of absence of a clinical effect, or when an exacerbation of the process occurs while the application of

1% pimecrolimus, it is possible to repeat to short-term courses of topical GCS with weak or moderate effects.

In patients with moderate from of AtD in case of disseminated process with mild or strong inflammatory activity (SCORAD 20 to 40 points) It is recommended to prescribe mild or strong topical GCS therapy and the most effectives medicines for this type of therapy are followings: 0.1% methylprednisolone acetate, 0.1% mometasone furoate, betamethasone valerate, 0.1% hydrocortisone 17-butyrate. There is also an indication for the use of 1% pimecrolimus cream especially in problem areas of the skin of the face, neck and wrinkles of these patients. The use of topical GCS is possible for a longer period - up to 4-6 weeks, courses with 1% pimecrolimus cream - until complete disappearance of symptoms.

There is an indication for the appointment of 03% tacrolimus ointment in 2-16 years old children with moderate and severe forms of AtD. According to indications and therapy regimen on the first stage of the treatment tacro-limus ointment should be applied twice a day (from 3 to 6 weeks), then the supportive topical therapy continues for 3-12 months on the damaged areas of the skin by rubbing tacrolimus ointment twice a week with emollients.

Clinical signs in the form of grouped papules, peeling, lichenification, infiltration, dry skin, hyperkeratosis predominate in patients with severe form of AtD (SCORAD index is more than 40 points), complications are fixed in the form of episodes of transient erythroderma, lymphadenopathy. In such patients there is an indication for the inclusion of systemic GCS in complex therapy - for up to 7 days, at a dose of 0.75-1.0 mg / kg body weight; application of photochemotherapy on a 4-day scheme (10-15 procedures during the course with internal application of photosensitizer) after decreased activity of clinical signs of dermatosis and in the absence of contraindications for elderly patients is possible. Lying of therapeutic means to patients receiving topical GCS and light therapyshould be performed no earlier than 1 hour after the procedure.

The mean SCORAD index in the group of children with AtD before therapy was 38.6±1.8 points. Treatment of children by using

Protopic (tacrolimus) ointment 0.03% twice a day showed positive dynamics of clinical symptoms of AtD already on days 3-4 of the start of treatment: itching of the skin, hyperemia, swelling in the area of rashes decreased. The mean SCORAD index in all patients was decreased in 14^{th} day of the treatment and was 50.6±5.4%. As the observation shows,the degree of expression of the symptoms of the disease is further reduced on the next 14 days and on the 28^{th} day of the treatment the average SCORAD index in this group of children was 9.8±1.4 points and achieved regression of the severity of the disease was 82.2±4.6%. Active therapy with 0.03% tacrolimus ointment 2 times a day of children with AtD allowed to achieve clinical remission and significant improvement in 41 (85.4±5.1%) patients, and to maintain this condition after the end of the supportive course. During the observation of children with AtD it was detected that 2 months after supportive care (day 88) deterioration of the skin was occured in 1 patient, after 3 months (day 118) - in 2 patients; the SCORAD index was slightly increased, however, the SCORAD index remained within 50 points compared to pre-therapy levels.

Application of enterosgel enterosorbent as part of anti-allergy and antifungal therapy during 2-3 weeks in children with AtD complicated by fungal infection leads to the following short-term and long-term positive results: clinical remission on the 14th day of therapy; prolongation of remission and reduction of recurrence. Inclusion of Enterosgel enterosorbent in the treatment program of ATD helps to reducing the level of sensitization and it is approved by a decrease in the amount of total IgE in the blood serum and allergen-specific IgE against food allergens.

Systemic endotoxinemia has been identified in children AtD. During the exacerbation of ATD, the amount of plasma endotoxin was higher than in the control group, and decreased in the priod of remission, but it does not reach indexes of physiological endotoxinemia. The level of plasma endotoxin depends on the severity and activity of the skin process.The presence of systemic endotoxinemia is an indication for enterosorption.Including of Enterosgel, which has a complex effect, in traditional anti-allergy therapy leads to shortenin of the period of exacerbation by 1.6 times

(from 20 to 12 days), to a decrease in the SCORAD index by 4.9 times against the background of a decrease in plasma endotoxin levels. Conducted examinations showed that basic therapy prevents the clinical signs of AtD in children, especially in the mild form of the disease, has a mild therapeutic effect, reduces the activity and degree of allergic inflammation of the skin without significantly changing the mechanisms of immune development of AtD. Significant changes are observed in the balance of IL-4, IL-13 and IFNγ in case of atopic dermatitis and production of these cytokine doesn't depend on duration of basic therapy.

It is known that colonization of the skin with Staphylococcus aureus occurs in more than 90% of patients with AtD and it is able to exacerbate or maintain the inflammatory process of the skin through the secretion of a number of toxins-superantigens that stimulate large amounts of T-cells and macrophages. Nearly half of patients with AtD produce IgE against staphylococcal toxins. These approaches confirm that, the local production of staphylococcal enterotoxin on the surface of the skin can cause IgE-conditioned secretion of histamine from mastocytes and may act as a trigger of the itching cycle. This situation can lead to exacerbation of clinical symptoms of the disease. This mechanism is the basis of frequent secondary infections of the skin in children with AtD and determines the need for topical use of antibacterial and antifungal drugs.

So, proposed approaches for treatment of patients with severe AtD allows timely prevention of infection and inflammation of the skin, prevention of severe AtD and achieving lasting remission of the disease. Development and improvement of treatment program for children with AtD are focused on preventing the development of dangerous aggravated forms of the disease.

CONCLUSION

1. As the results of the epidemiological examination it was determined that during 2014 – 2019 years the prevalence rate of atopic dermatitis among children with skin diseases in Baku citywas 12.0 ± 1.8%. In the main group of examined children girlsprevailed in comparison with boys (respectively, 76 girls –

67.9% and 36 boys – 32.1%; p<0.001). Among sick children the quantity of patients aged 1-5 years (41.1±4.6%) and 6-10 years (42.9±4.7%) was more than those aged 11-15 years (p<0.001). Share of 1-5 years old girls was higher for 43.4±5.7% and 44.4±8.3% among 6-10 years old girls [5,9].

2. More patients with severe AtD (45 patients, 70.2±5.9%, p <0.001) were in the form of the disease aggravated with a secondary infection, and patients with moderate form of disease were more in group not aggravated with a secondary infection (31 patients, 64.6±6.9%, p<0.001). The sever e form of the disease was 38.9±6.3% among boys and 61.1±6.3% (t = 2.50; P <0.05) among girls. AtD manifested in 41.9±4.7% of children with erythematosus-squamous form and 58.1±4.7% with erythematosus-squamous form with lichenification. concomitant diseases have been identified in 106 patients with AtD (94.6±2.1%) [1,2,7,8].
3. The risk factor of AtD were divided into groups as the result of conducted study [4,5,8]:

– Uncontrolled and conditionally controlled pre- and perinatal risk factors leading to the development of the disease.
(It was detected that, in group of children with AtD aggravated with a secondary infection 60.9±6.1% (39 children) were born on time, 81.2±4.8% (52 children) were born by caesarean section, but in the second group these indicators were respectively 85.4±5.1%, p<0.01 (41 children) and 62.5±7.0%, p <0.05 (30 children).)

– Conditionally managed and managed postnatal risk factors that cause disease exacerbation and affect its course after diagnosing AtD.
It was detected that, in the group of children with AtD aggravated with a secondary infection 18.6±4.9% (12 children) of breast feedings longed under 1 year, 12.5±4.6% (8 children) of children suffered from adenoiditis, but in the second group these indicators were restively 91.7±3.9%, p <0.001 (44 children) and 29.2±6.5%, p<0.05 (14 children). As the result of conducted research works it was determined that the role of

bacterial and fungal infections as a postnatal risk factor aggravating the course of AtD is great (staphylococcus aureus - 87.5±3.1%, staphylococcus epidermidis - 77.6±3.9% , fungal infection of the skin - 25.0±4.1%, non-staphylococci and their association with fungi were found in 18.0±3.6% of cases).

4. Spectrum of cytokines, except of IL-17F in children with AtD (13.1% of children in the main group and 8.8% of children in the comparison group) did not differ from the comparison group. Generally, a similar trend is observed in differences in the amount of cytokines during remission. The levels high of IL-4 and IL-10 were observed, in this case the decreasing of IFN-γ in the remission period differed more pronounced than in the general group of patients with AtD even in period (45.0±1.48 and 15.1±1.87, t=12.57; P<0.001). In our study, in the acute period and period of remission statistically significant differences in the amount of T-reg sells were found in a group of healthy children and a group of children with AtD. A sharper distribution of indicators was observed in the group with exacerbation of ATD.

   The questionnaire on life quality indicators covering medical, social and psicological aspects was developed adopting to children with AtD and quality of life of these children was low even in remission period, and was detected as 13.7 points. In this case, the psychological sphere suffers more and it indicates that the child needs psychotherapeutic assistance [3,6].

5. An algorithm of preventive and curative measures in children with AtD has been developed for more accurately determining of AtD risk factors during screening studies. Risk syndromes characterizing the neurological and immunological component of the pathogenesis of ATD have been addressed for detecting of risk factor of development of AtD. It was concluded that the proposed algorithm should be used and a team of several experts should observe the identified relevant risk factors for being more confident that there is a real risk of developing AtD [9,10,13]. Using the algorithm of therapy of AtD patients based on the principle of step therapy, reduced the demand for in the

treatment of patients. Comparing with long time treatment with TGCSs joint appointment of calcineurin topical inhibitor and topical antibacterial and antifungal drugs reduced the incidence of complications such as secondary infection. In children with AtD the average indicator of the SCORAD index was 38.6±1.8% before the therapy with a topical calcineurin inhibitor and regression of the disease severity indicator up to 82.2±4.6% was achieved on the 28th day of the treatment. In children with AtD aggravated by fungal infection, prescribing of enterogel enterosorbent led to shortening of the exacerbation period for 1.6 times, decrease in the SCORAD index for 4.9 times, and creation of conditions for the reduction of the level of level of sensitization and reducing of the number of relapses.

PRACTICAL RECOMMENDATIONS

1. Achieving effective control over condition of patients with AtD and improving their quality of life is possible onle by complex approach to the treatment, taking into account age features of the clinical picture of the disease, severity and stage of the course, the presence of respiratory manifestations of atopy and concomitant pathology.
2. Risk groups among pregnant women should be detected. There should be serious control over concomitant chronic and allergic diseases, medication during their treatment, caesarean section cases andit is necessary to take measures to reduce its level. Carrying out educational work among pregnant group from the risk group allows to reduce the incidence of aggravated forms of AtD.
3. For correct assessment of immunological status it is necessary to monitor indicators in the dynamics of the disease (to investigate the causal factors).
4. The saprophytic flora in the skin is activated and becomes resistant to treatment due to reduced system reactivityagainst the background of immunological changes in children with AtD. In this regardtt is recommended to use antiseptics and

antifungals in local treatment in any stage of the disease taking into account the clinical form and age of the child.

5. Step-by-step approach to the treatment of AtD intends including of different therapeutic methods in the treatment regimen depending on the severity of the disease. For development of efficiency of the treatment there should be individual approach to each patient. The treatment method should be indicated after studying of risk factors, and detecting of age, clinical form, severity of the disease, immunological status.

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LIST OF ABBREVIATIONS

AtD	- atopic dermatitis
ASSI	- allergen specific sublingual immunotherapy
CIC	- circulating immune complexes
EASI	- Exzema Area and Severity Index
PI	- Phagocytic index
LQ	- Life quality
ICD	- International Classification of Diseases
IgA	- Immunoglobulin A
IgE	- Immunoglobulin E
IgG	- Immunoglobulin G
IgM	- Immunoglobulin M
IFN-γ	- interferon-gamma
İFA	- immune enzyme analysis
IGA	- Investigators' Global Assessment
IL-1β	- interleukin -1β
IL-1ra	- interleukin -1 receptor antagonist
IL-4	- interleukin 4
IL-6	- interleukin 6
GIT	- gastrointestinal tract
PAN	- phagocytic activity of neutrophils
NGT-test	- Test of restoration of nitro-blue tetrazole in the cytoplasm of neutrophils testi
SCORAD	- Scoring of Atopic Dermatitis
TGF-β1	- Transforming growth factor - beta
FIP	- the frequency of the inspiratory phase
TGCS	- topic glucocorticoid steroids
TNF-α	- tumor necrosis factor
ChPR	- chain polymerase reaction

The defense will be held on 28 October 2022 at 14. 00 at the meeting of the Dissertation council FD 2.11 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev.

Adress: AZ1012, Muzaffar Hasanov Street 35, Baku city
Dissertation is accessible at the Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev.

Electronic versions of dissertation and its abstract are available on the official website http://www.adhti.edu.az .

Abstract was sent
to the required addresses on " 23 " September 2022

Signed for print: 29.04.2022

Paper format: 60 x 84 1/16

Volume: 38727
Number of hard copies: 20