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ASSOCIATION BETWEEN ATOPIC AND NON-ATOPIC DISEASES AT CHILDREN

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Ключевые слова: *дети, аллергические заболевания, атопический марш, ассоциация, неатопические болезни, пищеварительная система*

Abstract. Association between atopic and non-atopic diseases at children. Abaturov O., Dytiatkovsky V., Naumenko N., Kulieva A., Bovsunovska K., Filatova I. *The paper presents the data of the association analysis between the diseases composig the atopic march (AM) in children – atopic dermatitis (AD), seasonal rhinoconjunctivitis (SARC) and perennial allergic rhinitis (PAR), bronchial asthma (BA), with non-atopic allergic diseases – acute and recurrent urticaria (AcU/RecU), Quincke edema (QE), and also with diseases of the digestive system (DS) – functional disorders of the biliary system (FDBS) and reactive pancreatitis (RP). The association between AD and food allergy (FA) in children has been determined, which is recorded as a direct association. A direct association was established between chronic infectious diseases of the upper respiratory tract and the PAR as well as BA. The lack of association between atopic and non-atopic allergic diseases had been confirmed. The association between FDBS and RP and non-atopic allergic diseases in children had been determined – AcU/RecU, QE.*

Реферат. Ассоциация между атопическими и неатопическими аллергическими болезнями у детей. Абатуров А.Е., Дитятковский В.А., Науменко Н.В., Кулиева А., Бовсуновская К., Филатова И.А. *В статье приведены данные анализа ассоциации между болезнями, составляющими атопический марш (АМ) у детей – атопическим дерматитом (АД), сезонным аллергическим риноконьюнктивитом (САРК) и круглогодичным аллергическим ринитом (КАР), бронхиальной астмой (БА) – с неатопическими аллергическими болезнями – острой и рецидивирующей крапивницей (ОК/РК), отёком Квинке (ОКв), а также болезнями пищеварительной системы (ПС) – функциональными расстройствами билиарной системы (ФРБС) и реактивным панкреатитом (РП). Определены ассоциации между АД, АМ и пищевой аллергией (ПА) у детей, что зафиксировано в виде прямой корреляционной связи. Определена прямая ассоциация между хроническими инфекционными заболеваниями верхних дыхательных путей и САРК, КАР и БА. Подтверждено отсутствие связи между атопическими и неатопическими аллергическими болезнями. Выявлены ассоциации между ФРБС, РП и неатопическими аллергическими болезнями у детей – ОК/РК, ОКв.*

Atopic diseases at children (AlD) include atopic dermatitis (AD), seasonal allergic rhinoconjunctivitis (SARC), perennial allergic rhinitis (PAR) and bronchial asthma (BA). Non-atopic allergic diseases are mainly represented by acute and recurrent urticaria (AcU/RecU) and Quincke edema (QE). In recent years, the prevalence of AlD has increased and currently affects about 20% of the world's human population [9]. Recently there had been developed the concept of atopic march (AM) from early childhood to school age and adolescence [3]. The mechanism of AM development is always an individual combination of risk factors and represents a linear progression of AD-SARC/PAR-BA. The essence of the combination is the interaction of genetic and environmental factors. AM development can take place by atopic mechanisms with/or without environmental triggers that will lead to transformation AD into the respiratory forms of AlD [4]. Thus, according to van der Hulst et al., the frequency of AD that began in early childhood into BA does not exceed 30% [8]. In view of the strong family predisposition for AlD associated with the genotype, the gradual decrease in exposure to the heterogeneity of microorganisms over the past decades has led to immune dysregulation in such populations, increasing the incidence of hypersensitivity – AlD- and autoimmune diseases [5].

The main mechanism of pathogenesis of AlD in most patients is IgE-mediated allergic inflammation. At the same time, in 10-30% of patients, elevated IgE levels are not recorded. This confirms the hypothesis of the complex nature of AD and other AlD represented by other immune and non-immune (pseudoallergic) mechanisms of inflammation. Triggers of non-allergenic nature, which are most often recorded as causative of AD, are dietary abuse, uncompensated psycho-emotional stress, tobacco smoke, xenobiotics, industrial pollutants. Dietary abuse separately and in combination with uncontrolled use of xenobiotics lead to dyspepsia syndrome in the intestine, which is the trigger mechanism for the AcU/RecU and QE. The main nosological forms of the pathology of the digestive system are functional disorders of the biliary system (FDBS) and reactive pancreatitis (RP).

Despite the large number of studies on AD comorbidities that provide data for analyzing AD complications, such as neurotic disorders, sleep disturbances, bleeding gums, toothache, etc., but not there is analyzed comorbid states from the digestive system, which can be internal triggers of AD development in particular and AM in general [2, 6]. Currently, the main internal factors for triggering AD with the risk of transformation in BA is food sensitization and mutation of the filaggrin gene [7]. Although some studies attempt to establish a causal relationship between AlD and the change in the qualitative and quantitative composition of the gut microbiome [10], there is still currently little data on the association between AlD, FRBS and RP.

The purpose of the study was to determine associations between atopic (AD, SARC/PAR, BA), non-atopic (AcU/RecU, QE) allergic diseases and diseases of the digestive system (FRBS and RP) at children from 0 to 18 years old.

CHARACTERISTICS OF PATIENTS AND METHODS

We analyzed the case histories of 790 children with AlD, who were hospitalized to the Dnipro City Children`s Allergology Center during the calendar year 2016. The mean age of hospitalized children was 9.5±0.15 years (median – 9.0), the youngest patient was 10 months old, and the eldest – 17 years. The distribution of patients by age group was heterogeneous: 0-3 years – 49 (6.20%), 3-6 years – 181 (22.91%), 7-11 years – 285 (36.08%), 12-18 years – 275 (34.81%). WE had been selecting the case histories of children with AM nosologies AM (AD, SARC/PAR, BA as well as AcU/RecU, QE. Among the main diagnosis SARC had been dignosed in 385 (48.73%) cases, PAR – 366 (46.33%), AD – 73 (9.24%), ACU/RECU – in 98 (12.41%), QE – 51 (6.46%), bronchial asthma (BA) in 223 (28.23%) cases, furthermore in half the patients (47.09%) there was a combination of different allergological nosologies. The incidence of causative factors of AlD at children was characterized by the polysensitization of one patient to several types of allergens, and had the following proportions: pollen sensitization – 74.56%, household to housedust mites (HDM) – 56.71%, to the epidermal allergens of the cat and dog – 31.27%, to fungal allergens – 17.22%, to medicinal preparations – 7.72%, to venom allergens – 5.95%, to food products – 2.15%.

Statistical processing was carried out using the licensed software Statistica v. 6.1 for Windóws (serial number AGAR909E415822FA). In the study of association relationships, the Spearman rank association ratios (R) were used with an estimate of their statistical significance by Student's criterion (t). The critical significance level of the association ratio (p-level) was taken as <0.05. The presence of an association between different diseases, sensitization, or other comorbid states has been evidenced by positive association ratio (direct relation), the absence of interaction – by a negative coefficient. The association strength was evaluated as weak at $|R|<0.3$, moderate – at $0.3\leq|R|\leq0.7$, strong at $|R|>0.7$ [1].

RESULTS AND DISCUSSION

According to the results of the association analysis, the peculiarities of interactions between etiological factors, comorbid conditions and other factors within various AlD at children were established.

Atopic dermatitis. Analysis of the combination of AD with other parameters of the disease confirms the absence of correlation between the urticaria and AD as nosologies with different mechanisms of development (table 1). At the same time, a direct association between AD as the main manifestation of FA at children and digestive system (DS) diseases, in particular, FDBS and RP, had been established. This evidences the role of syndromes of dyspepsia and maldigestion, which are characteristic to FRBS and RP, and exacerbation of AD at children.

Table 1

Association of atopic dermatitis with different factors

Factor	Spearman R	t(N-2)	p-level
Urticaria	-0,080	-2,261	0,024
FDBS	0,139	3,949	0,000
RP	0,070	1,975	0,049
DS-comorbidities total score	0,145	4,123	0,000

Acute/recurrent urticaria

Particular attention should be paid to urticaria, since combining different mechanisms of pathogenesis, it does not compose AM. Thus all AM-nosologies – AD, SARC, PAR, BA – did not have a significant association to AcU/RecU. This allows us to confirm the fact that episodes of AcU/RecU do not accelerate the course of AM, do not cause the transformation of one form AM to another. In particular, it concerns AD, which, being an allergic disease affecting the skin, originates from another mechanism of pathogenesis – a direct association to ACU/RECU, according to the results of our study, is absent (table 2).

Table 2

Association of urticaria nosologies with different factors

Factor	Spearman R	t(N-2)	p-level
Age	-0,172	-4,913	0,000
Pollen sensitization	-0,400	-12,241	0,000
Household sensitization (HDM)	-0,237	-6,855	0,000
Food/drug/ insect venom sensitization	0,138	3,909	0,000
Epidermal sensitization (cat/dog/birds` feather)	-0,172	-4,890	0,000
SARC	-0,344	-10,280	0,000
PAR	-0,311	-9,190	0,000
AD	-0,080	-2,261	0,024
Quincke edema	0,104	2,943	0,003
BA	-0,227	-6,557	0,000
FDBS	0,180	5,139	0,000
RP	0,121	3,410	0,001
DS-comorbidities total score	0,181	5,157	0,000
Sensitization total	-0,371	-11,211	0,000

The absence of general mechanisms of pathogenesis was also confirmed within studying the etiological spectrum of AcU/RecU – a significant direct association was determined only with food, drug and/or insect venom allergens – the traditional etiological spectrum in patients with AcU/RecU. In this case, there was no direct association with the traditional AM-nosologies groups of allergens – pollen, HDM and pets' epidermal.

We have determined the reverse association of AcU/RecU with the age of sick children, which indicates a higher incidence of urticaria at younger ages. Thus, the prevalence of ACU/RECU among children under 6 years of age is 20.87% (48 out of 230 cases), at the age of 6-11 years – 9.12% (26 out of 285 cases), at the age of 12-18 years – 8.73% (24 out of 275 cases) at $p<0.001$ compared with preschool children. A direct association was established between AcU/RecU and QE which often interact with each other. It is necessary to note the confirmation of hypothesis of the association of disorders of the digestion process and urticaria, which demonstrate approximately identical strengths of direct associations between the FDBS, RP, and the general level of morbidity of the DS and AcU/RecU.

Quincke edema (QE)

Pathogenetically associated to AcU/RecU is a Quincke edema, which often occurs at the same time with urticaria. According to the correlation analysis, there is a positive correlation between QE and urticaria, as well as with food and insect venom sensitization which confirms the hypothesis about the non-atopic nature of QE mechanisms (table 3).

Table 3

Association of Quincke edema forms with different factors

Factor	Spearman R	t(N-2)	p-level
Age	-0,093	-2,611	0,009
Pollen sensitization	-0,238	-6,888	0,000
Household sensitization (HDM)	-0,177	-5,054	0,000
Epidermal sensitization (cat/dog/bird feather)	-0,120	-3,387	0,001
Food sensitization	0,098	2,755	0,006
Insect venom sensitization	0,360	10,835	0,000
Sensitization total score	-0,142	-4,033	0,000
SARC	-0,205	-5,868	0,000
PAR	-0,213	-6,122	0,000
AcU/RecU	0,104	2,943	0,003
BA	-0,142	-4,023	0,000
ARVI (rhinopharingitis/bronchitis)	0,077	2,158	0,031
FDBS	0,078	2,206	0,028
DS-comorbidities total score	0,079	2,234	0,026

The presence of QE reverse association with age points to the danger of this nosology – more often it occurs at young children (up to 6 years old). The high level of mucosal vascularization and the small diameter of the sub-vocal space of the vocal box space leads to a high risk of occurrence of QE in larynx, which is a life-threatening condition. There was no reliable direct association with pollen, HDM or epidermal sensitization. The etiological spectrum was represented by food and insect venom allergens, which confirms the emergence of QE after alimentary abuse and insect bites.

Seasonal allergic rhinoconjunctivitis (SARC)

According to the association analysis, it is established that SARC has a direct association with the age of the studied children – it`s frequency increases with age (table 4). Thus, the prevalence of SARC among children under 6 years of age is 30.43%, at the age of 6-11 years it is 55.44%, at the age of 12-18 years, it is 57.09% at $p<0.001$ compared with the

children of preschool age. A strong direct association exists between pollen sensitization and SARC (R=0.831, p<0.001), which proves the dominance of allergy to plant pollen in the etiology of SARC as the most common form of pollinosis. Unexpected there was to be determined the association between the sensitization to the HDM (n Der p1, n Der p2), the epidermal allergens of the cat, the dog and the bird feathers and SARC - its value is 10 times less than the association with pollen sensitization, but the direct nature of it indicates the presence of patients with combined forms of allergy: the pollen one that causes SARC and to mites of household dust, cats, dogs and birds that cause the PAR.

Table 4

Association of seasonal allergic rhinoconjunctivitis with different factors

Factor	Spearman R	t(N-2)	p-level
Age	0,209	5,988	0,000
Pollen sensitization	0,831	42,006	0,000
Household sensitization (HDM)	0,080	2,250	0,025
Food/drug/insect venom sensitization	-0,119	-3,376	0,001
Epidermal sensitization (cat/dog/bird feather)	0,085	2,404	0,016
PAR	-0,164	-4,678	0,000
BA	-0,116	-3,288	0,001
Bronchial obstruction syndrome (BOS)	0,235	6,773	0,000
FDBS	-0,113	-3,193	0,001
RP	-0,072	-2,037	0,042
DS-comorbidities total score	-0,116	-3,265	0,001

Controversial data have been obtained regarding the association of BA, SARC and PAR – there was a significant negative association between them, that is, pollinosis in SARC format had been identified more often separately from the PAR and BA of a non-pollen etiology. At the same time, a direct asociation had been established between SARC of pollen etiology and the emergence of a bronchial obstruction syndrome (R=0.235, p<0.001), which indicates the transformation of the allergic rhinoconjunctivitis into BA in the course of AM at children. Concerning the combination of SARC and DS impairments, then the negative associations ratios indicate that there are no such connections.

Perennial allergic rhinitis (PAR)

Analyzing the data on the association of PAR with other factors, we have received a direct one with age – the incidence of PAR is increasing with the increase in the age of children as the form of AM progression (table 5). The etiological spectrum of the PAR was represented by reliable direct associations with HDM, the cat, dog and birds feathers allergens, and fungi of Alternaria, Aspergillus genera placed in this roster in order of decreasing the association strength.

Unlike SARC, a frequent combination with BA (R=0.145, p<0.001), as well as with inflammatory-proliferative diseases of the nasal cavity (adenoid vegetations, gaimoritis/ethmoiditis, etc.) is characteristic for PAR. Thus, it can be stated that the transformation of the PAR, as a chronic inflammation of the mucous membrane of the nose, not only into BA in the AM course, but also in the ENT pathology. The negative association between PAR and ARVI (acute rhinopharyngitis and bronchitis) and the pathology of the DS (FDBS) indicates that there is no significant association between the PAR and these nosologies at s separate patient.

Bronchial asthma is the final stage of AM, therefore, the establishment of its associations with other nosologies of AM is important for developing the methods of treatment and prevention of AM in children. The analysis of data in table 6 showed a direct association between the age of children and the incidence of asthma (R=0.284, p<0.001). That is, this diagnosis is more common in schoolchildren and adolescents – in 14.35% than at children under the age of 6 years – in 25.26% of children 6-11 years old (p<0.01) and in 42.91% of children aged 12-18 years old (p<0.001 in comparison with other age

groups), confirming the hypothesis of asthma as the final stage of AM development. The etiological spectrum of asthma was mostly represented by HDM-allergens. Among all the forms of AlD that we had studied at children, a reliable direct BA association was established only with the PAR (R=0.145, p<0.001), while other AM nosologies (AD, SARC) did not demonstrate a direct association with asthma.

Table 5

Association of perennial allergic rhinitis with different factors

Factor	Spearman R	t(N-2)	p-level
Age	**0,088**	**2,479**	**0,013**
Household sensitization (HDM)	**0,228**	**6,562**	**0,000**
Epidermal sensitization (cat/dog/bird feather)	**0,195**	**5,580**	**0,000**
Fungal sensitization (Alternaria alternata, Aspergillus fumigatus)	**0,107**	**3,025**	**0,003**
SARC	**-0,164**	**-4,678**	**0,000**
BA	**0,145**	**4,110**	**0,000**
BOS	**-0,138**	**-3,898**	**0,000**
Inflammatory-proliferative disorders of the nasal cavity (adenoid vegetations/ gaimoritis/ethmoiditis)	**0,101**	**2,841**	**0,005**
ARVI: acute rhinopharyngitis/bronchitis	**-0,101**	**-2,843**	**0,005**
FDBS	**-0,075**	**-2,111**	**0,035**
DS-comorbidities total score	**-0,071**	**-1,991**	**0,047**

Controversial data had been found on association with other nosologies. Thus, ARVIs, which are the main trigger of asthma at preschoolers (Okhotnikova et al., 2011), did not show a significant direct association with asthma; instead, ENT pathology (tonsillitis and / tonsils hypertrophy) had a direct association with BA. In our opinion, this is due to the sensitizing effect of bacterial cells, the concentration of which increases as a result of chronic carrying in the mucous membranes of the oral cavity within these nosologies.

Table 6

Association of bronchial asthma with different factors

Factor	Spearman R	t(N-2)	p-level
Age	**0,284**	**8,313**	**0,000**
Household sensitization (HDM)	**0,081**	**2,268**	**0,024**
Food sensitization	**-0,076**	**-2,141**	**0,033**
SARC	**-0,116**	**-3,288**	**0,001**
PAR	**0,145**	**4,110**	**0,000**
AcU/RecU	**-0,227**	**-6,557**	**0,000**
QE	**-0,142**	**-4,023**	**0,000**
Tonsillitis/tonsils hypertrophy	**0,114**	**3,211**	**0,001**
BOS	**-0,146**	**-4,134**	**0,000**
ARVI: acute rhynopharingitis, bronchitis	**-0,072**	**-2,021**	**0,044**

The study results showed different formats of associations between AM nosologies and other AlD and comorbidities. Thus, direct association between AD, FDBS and RP points to dyspepsia syndrome as the main etiopathogenetic mechanism of development of the food intolerance and, as a result, its transformation into food allergy (FA). SARC was found more frequently in older children (6-11 years old, 12-18 years old) and had a significant direct association with plants` pollen as the main etiological factor for pollinosis. At the same time, weak, but significant associations of SARC with HDM and pets` epidermal allergens appear to be interesting, indicating the association of SARC and PAR at the same patient as a consequence of co-sensitization in the course of chronic allergic inflammation with hyperproduction of general and specific IgE. The direct correlation of SARS with bronchial obstruction syndrome as a complication of acute bronchitis at children points at a tendency for the transformation of atopic disease into BA in the form of descending the inflammatory process from the mucous membranes of the upper airways and the eye bulb down to the mucous membranes of the bronchi. The continuation of AM goes on in the form of a PAR, the frequency of which increases with age, and the etiological spectrum is confirmed by sensitization to typical allergen groups – HDM, pets`epidermal allergens and fungal major allergens Alt a1(mold genera Alternaria alternata). Interestingly, the direct association of PAR had been found not only with the BA, but also with proliferative-inflammatory diseases of the nasal cavity (adenoid vegetations, ethmoiditis, gaimoritis), indicating a direct association between chronic inflammation of the mucous membrane and transformation of the inflammatory process into an allergic involving Th-2 cells and IgE. The trend of causative associations is maintained as well in BA case – more often BA occurs early schoolers and adolescents and is associated with HDM-sensitization. The presence of a direct associations between BA with chronic tonsillitis and/or tonsils hypertrophy reveals, in our opinion, a mixed mechanism of the BA pathogenesis with the involvement of the pathogenic microflora of the respiratory tract.

A separate group had been being urticaria and Quincke edema. In our study, there had been no significant direct association with atopic diseases – AD, SARC/ PAR, BA. This indicates the difference in pathogenesis mechanisms of development of those AlDs from atopic diseases, which confirms the independence of AM in children from Acu/Rec and QE. In this case, statistically significant asdociation between those nosologies and typical etiological factors was revealed. Thus, AcU/RecU had a direct association with food, drug and insect venom sensitization as well as with QE, and clinically – with FDBS and RP. In turn, QE was reliably associated with AcU/RecU, food and, most of all, with an insect venom sensitization (insect bites). This sequence is continued by the direct association of AcU/RecU and QE with DS-disorders - FDBS and RP. Concerning the revealed interrdependance of QE with ARVI (rhinopharyngitis/bronchitis), further clinical and statistical studies are needed for it's explanation.

CONCLUSIONS

1. Atopic dermatitis is the first step of AM and is caused, first of all, by food allergens.
2. One of the FA and AM triggers at children are the comorbid states of the digestive system and, in particular, FDBS.
3. Within achieving by a child sick with AM the school-age disease is being transformed into SARC and/or PAR with typical sensitization spectrum – to plants`pollen (SARC), HDM, epidermal and fungal (PAR) allergens, respectively.
4. SARC and PARs have a statistically significant BA transformation trend.
5. Chronic infectious-inflammatory diseases of the upper respiratory tract have a direct association with the development of the PAR and BA. Chronic ethmoiditis and sinusitis aggravate the course of PAR, chronic tonsillitis and tonsils hypertrophy that of BA.
6. Acute and reccurent utricaria as well as Quincke edema compose a separate group of AlD that are pathogenetically and clinically interdependant and have no reliable association with AM diseases.
7. There is a direct association between nosological forms of urticaria and Quincke edema and diseases of digestive tract – FDBS and RP.

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