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Pre-school wheezing: from phenotypes to natural evolution

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Abstract

The study aimed to investigate the clinical and immunological characteristics of different phenotypes of wheezing syndrome in early-age children. A controlled, non-randomized clinical trial was conducted involving 120 children with wheezing symptoms, aged between 5 and 7 years, divided into two groups: patients with episodic wheezing and patients with multi factorial wheezing syndrome. The study found that 66.7% of the patients had multi factorial wheezing syndrome, while 33.3% had episodic wheezing. Children with multi factorial wheezing syndrome had a higher incidence of rhinitis, hay fever, and allergic skin damage than those with episodic wheezing. Additionally, 72% of patients with multi factorial wheezing syndrome had a heavy hereditary anamnesis. Allergic reactions were present in 98.7% of patients with multi factorial wheezing and 77.8% of children with episodic wheezing. The study did not observe any significant difference in the age of onset of the disease between the two groups. The causes of disease exacerbation in the multi factorial wheezing group were mainly viral infections and allergens, while in the episodic wheezing group, the primary trigger was viral infection. The study concluded that evaluating multivariate clinical features and using flexible mathematical approaches are necessary to improve the classification of wheezing phenotypes, which would help in individual phenotypic therapy.

KEYWORDS: wheezing in children; allergy; respiratory viral infection

Introduction

Wheezing is a common respiratory symptom in young children. According to population studies, one in three children will experience at least one episode of wheezing by the age of three and by age six this rate rises to nearly 50%. Despite the high prevalence of wheezing in early-age children, in 60% of cases, wheezing symptoms are no longer observed in adulthood. In some cases, early onset of recurrent wheezing is associated with persistent asthma and changes in lung function in adulthood.

In clinical practice, it is difficult to classify children with wheezing into mutually exclusive groups. Despite the complexity, defining wheezing phenotypes and studying their characteristics is important both for research and clinical practice as a basis for individual phenotypic therapy. To improve the classification of wheezing phenotypes, it is necessary to evaluate multivariate clinical features and use flexible mathematical approaches.

Aim of research

Study of clinical-immunological characteristics of different phenotypes of wheezing syndrome in children of early age.

Material and Methods

A single-stage, controlled, non-randomized clinical trial was conducted. 120 patients with wheezing were included in the study. According to the triggers, patients were divided into two groups: patients with episodic wheezing (the main trigger is a viral infection) and patients with multi factorial wheezing syndrome (in addition to the viral infection, other factors are also triggers: allergens, tobacco, laugh, crying, cold air, etc.).

Inclusion criteria Age of patients between 5 and 7 years, episodes of wheezing syndrome recorded in the outpatient card (probable diagnoses: obstructive bronchitis, allergic bronchitis, bronchiolitis) and informed consent of the parents for the patient's participation in the study.

Exclusion criteria: Receiving antihistamine drugs and corticosteroids during the last 3 months; Concomitant somatic pathology (congenital malformation of respiratory

and cardiovascular system, nasopharyngeal anomaly, oncological pathology and others); Severe chronic infection.

The individual registration chart included detailed information on the onset and manifestation of disease symptoms, atopic history and information on concomitant somatic pathology.

The patients involved in the study had the level of total IgE antibodies determined in the blood serum by the immunoferment analysis, allergy skin test (prick test). The concentration of nitric oxide (FeNO) in exhaled air was determined. Microsoft Excel 2010 and SPSS/v18 software packages were used during the statistical analysis of the obtained results.

Results

120 patients ages between 5 and 7 years were examined (average age was 6.13±0.86 years). 32.5% of them were girls (39 patients) and 67.5% (91 patients) were boys. 95.8% of the examinees were Georgians. Current weight was 25.16±5.7 kg, length – 124.73±7.4 cm, and body mass index (cm) – 16.17 kg/m2. The first group included 80 patients with multi factorial wheezing syndrome (66.7%), and the second group consisted of 40 patients with episodic wheezing (33.3%).

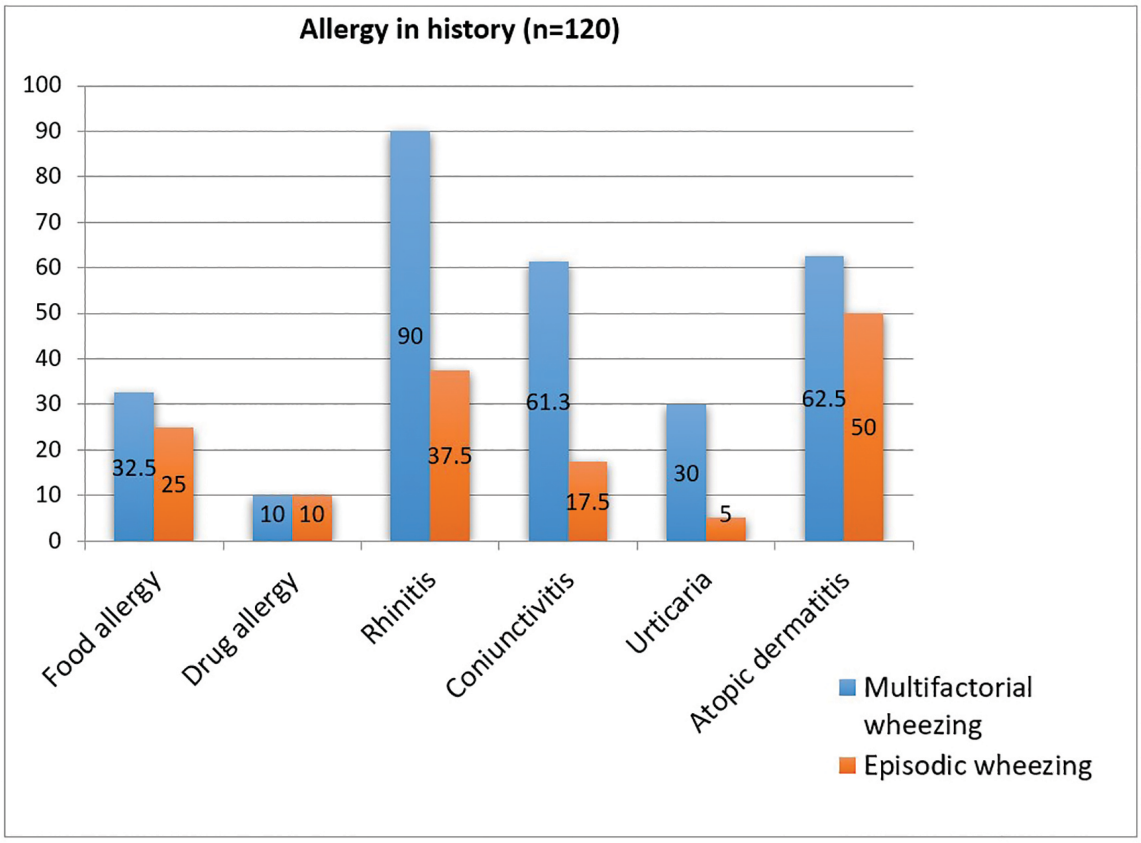
Hereditary allergy history of the studied contingent is presented in Table 1.

Table 1. *Hereditary burden of allergic diseases in patients with episodic and multi factorial wheezing syndrome (n=120)*

Hereditary allergic anamnesis	Wheezing		χ2	P
	Multifactorial (n=80)	Episodic (n=40)		
Rhinitis (Mother)	38 (47.5%)	15(37.5%)	0.714	3.598
Rhinitis (Father)	25 (31.3%)	8 (20.0%)	1.176	0.279
Hay fever (Mother)	35 (43.8%)	12 (30.0%)	1.578	0.209
Hay fever (Father)	24 (30.0%)	2 (5.0%)	8.402	0.004
Dermatitis (Mother)	29 (36.3%)	11(27.5%)	0.000	1.000
Dermatitis (Father)	15(18.8%)	4 (10.0%)	0.946	0.331
Drug allergy (Mother)	15 (18.8%)	3 (7.5%)	1.838	0.175
Drug allergy (Father)	6 (7.5%)	0	–	–
Food allergy (Mother)	14(17.5%)	4(10.0%)	0.662	0.416
Food allergy (father)	13(16.3%)	3(7.5%)	1.091	0.297

In most cases (72%) of patients with multifactorial wheezing syndrome a heavy hereditary anamnesis was observed. During episodic wheezing, this rate was 40% ((χ2-31.582, P-0.0001). During multifactorial analysis, rhinitis (mother-47.5%, father-31.3%), hay fever (mother-43.8%, father-30.0%) was present from both parents and hereditary load with allergic skin lesions (mother–36.3%). In cases of episodic wheezing, rhinitis (mother – 37.5%), hay fever (mother – 27.5%) and allergic skin damage (mother – 27.5%) also prevailed. 98.7% of patients with multifactorial wheezing and 77.8% of children with episodic wheezing had a history of allergic reactions ((χ2-13.105, P-0.001). Compared to other allergic reactions, the incidence of rhinitis ((χ2-34.279, P-0.001), conjunctivitis ((χ2-18.788, P-.0001) and urticaria ((χ2-8.402, P –0.004) was significantly higher in the multi factorial wheezing group.

Diagram 1



In terms of the age of onset of the disease no significant difference was observed between the comparable groups. The first episode of multi factorial wheezing was observed in 13 patients (16.3%) before 1year, under the age of 3 years – 48 patients (60%), and after 3 years – 19 patients (23.7%). In cases of episodic wheezing, 13 patients (32.5%) had a first episode before 1 year, 16 (40%) before 3 years, and 11 patients (27.5%) after 3 years. In most cases in both groups, the disease started between 1 and 3 years.

The causes of disease exacerbation in the multi factorial wheezing group were: viral infection (97.5%), tobacco (30.0%), strong odor (47.5%), physical activity (25.0%), cold temperature (32.5%), season (53.8%), plant pollen (36.3%) and dust mite (45.0%). Relatively rarely, the development of a wheezing attack was caused by contact with animals (20.0%), emotion (16.3%), humidity (21.3%) and climate changes (22.5%), in single cases – medications (10%), mold (11.3%) and food additives (7.5%). In 18 cases (22.5%) it was not possible to determine the provoking factor of the wheezing attack.

Clinical manifestations of wheezing phenotypes in early childhood are presented in Table 2.

Table 2. *Clinical manifestations of wheezing in the investigated groups (n=120)*

Symptoms of wheezing over 12 months	Wheezing		χ^2	P
	Multi factorial (80)	Episodic (40)		
>1 episode of cough per month	62 (77.5%)	8(20.0%)	33.947	0.000
Night cough	40(50.0%)	2(5.0)%	21.799	0.000
Dry night cough	43(53.8%)	3(7.50%)	22.214	0.000
Night symptoms	52(65%)	5(12.5%).	27.406	0.000
Cough >5 days	73(91.3%)	5(12.5%)	69.272	0.000
Sleep disturbance due to wheezing attack	53(66.35)	15(37.5%)	7.844	0.006
Wheezing after physical exertion	22 (27.5%)	6(15.0%)	1.683	0.195
Shortness of breath during cold	55(68.8)	12(30.0%)	14.704	0.000
Itching or rash in the last 12 months	48(60.0%)	14(35.0%)	5.711	0.017
Diagnosis of allergic manifestations	71(88.8%)	26 (65.0%)	8.236	0.005

During the last 12 months wheezing attacks occurred in 77 patients with multi factorial wheezing (96.3%), with a mean duration of 3.56 ±1.61 days. In the group of patients with episodic wheezing in the last 12 months, wheezing was noted in 14 cases (35.0%), with an average duration of 1.15 ±1.15 days.

Total IgE levels determined in all patients are presented in Table 3.

Table 3. *Indicators of total IgE in the examined contingent (n=120)*

Total IgE (IU/mL)	M	STDEV	MEDIANE	MODE	MAX	MIN
Multifactorial wheezing (n=80)	427.95	517.59	276.15	123	3085	8.92
Episodic wheezing (n=40)	161.23	220.08	106.60	26.79	943.60	7.49

Total IgE (IU/ml), unit

72 patients (97.5%) with multi factorial wheezing had increased total IgE level. The average rate was 427.95±517.59 IU/ml, which was almost 3 times higher than the data of children with episodic wheezing (161.23±220.08). In the group of children with episodic wheezing only 50% had elevated total IgE level. In both groups, IgE level changes were heterogeneous, with a wide range between maximum and minimum values, especially in multi factorial wheezing.

The quantitative changes of total IgE level in multi factorial wheezing were reliably correlated with allergic skin conditions (P-0.007) and food allergy (P-0.044), coexisting chronic tonsillitis (P-0.013), cough episodes 1 time per month (P-0.040), first episode of wheezing in response to viral infection (P-0.0001), animal contact (P-0.048) and exposure to dust mites (P-0.009). In cases of episodic wheezing, hereditary burden of allergic skin conditions (P-0.043), coexisting chronic tonsillitis (P-0.047) and bronchitis was significantly associated with IgE levels. (P-0.023), first episode of wheezing after viral infection (P-0.023) and atopic dermatitis in history (P-0.040). 20 patients with multi factorial wheezing (25%) had elevated nitric oxide content in exhaled air, with an average value of – 13.4±10.27 ppb. Nitric oxide levels in the episodic wheezing group ranged within the normal range, with a mean of 8.67±7.96 ppb. During multi factorial wheezing, sensitization to dust mites (67.5%), ragweed (22.5%), birch (22.5%), hazel (22.5%), oak (16.3%) and a mixture of herbs (15.0%) was detected, while those with episodic wheezing in some cases, sensitization to cat (2.5%) and dog allergens (2.5%) was observed.

Conclusions

As a result of the research, it was determined that the following differential-diagnostic features are characteristic of the phenotype of multi factorial wheezing syndrome: persistent course of the disease; Prevalence of night symptoms and high level of total IgE (427.95±517.59 IU/ml). The following differential-diagnostic features are characteristic of the episodic wheezing syndrome phenotype: intermittent course of the disease; Relatively low level of total IgE (161.23±220.08 IU/ml). Along with this, during multi factorial wheezing, rhinitis, hay fever and allergic skin conditions are more often found in hereditary allergic load, especially hay fever from the father side (χ2-8.402, P-0.004). Atopic reactions, specially rhinitis (χ2-34.279, P-0.001), conjunctivitis (χ2-

18.788, P-0.0001) and urticaria (χ2-8.402, P0.004) are present with a higher specific share compared to episodic wheezing. Knowledge of the determinants of wheezing phenotypes and clinical-immunological features, especially at an early age is crucial to ensure the effectiveness of therapeutic interventions. Wheezing identification and characterization of individual phenotypes with different prognoses and current studies will enable targeted interventions to reduce the burden of asthma in adulthood.

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