

THE RELATIONSHIP OF SPIROGRAPHIC PARAMETERS AND BRONCHIAL RESPONSIVENESS WITH ASTHMA CONTROL LEVEL IN CHILDREN (ACCORDING TO ACQ-5 AND ACT-C DATA)

UDC 616.248–053.2/7–073.17
Received 7.03.2013



T.I. Eliseeva, PhD, Associate Professor, the Department of Children Diseases¹;
E.V. Knyazeva, PhD, Tutor, the Department of Hospital Pediatrics²;
N.A. Geppe, D.Med.Sc., Professor, Head of the Department of Children Diseases³;
I.I. Balabolkin, D.Med.Sc., Professor, Corresponding Member of Russian Academy of Medical Science, Chief Research Worker of the Department of Pulmonology and Allergology⁴

¹Institute of Federal Security Service of Russian Federation, Kazanskoe shosse, 2, Nizhny Novgorod, Russian Federation, 603163;

²Nizhny Novgorod State Medical Academy, Minin and Pozharsky Square, 10/1, Nizhny Novgorod, Russian Federation, 603005;

³First Moscow State Medical University named after I.M. Sechenov, Trubetskaya St., 8, bld. 2, Moscow, Russian Federation, 119991;

⁴Scientific Children Health Centre of Russian Academy of Medical Science, Lomonosovsky Avenue, 2, Moscow, Russian Federation, 119991

The aim of the investigation was to assess the relationship of ACQ-5 and ACT-C indices and spirometric parameters in children with bronchial asthma (BA), reveal confidential intervals of these parameters typical for different levels of BA control. The BA levels were determined according to these questionnaires.

Materials and Methods. We examined 130 patients aged from 5 to 11 years with primarily atopic BA and different control level of the disease. In addition to routine examination, all children underwent the tests to determine BA control level using Asthma control questionnaire — 5 (ACQ-5) and Childhood Asthma control test (ACT-C). Spirometric examination was performed using Master-Screen Pneumo (Jaeger, Germany). Bronchial hyperresponsiveness was studied in tests with physical load (veloergometer Kettler AX1). The test with bronchial spasmolytic was used in children with exacerbation of the disease.

Results. According to ACQ-5, 90 children had complete control of the disease symptoms (ACQ-5<0.75 scores), 17 children — partial control (0.75<ACQ-5<1.5 scores), and 23 children — no BA control (ACQ-5>1.5 scores). According to ACT-C, in the same children, 95 children had controlled BA course (ACT-C≥20 scores), 35 patients — lack of control (ACT-C≤19). The correlation between ACQ-5 and ACT-C was –0.62, when $p<0.00001$.

The control level assessment according to ACQ-5 showed the average values of forced expiratory volume in 1 s (FEV1) in patients with complete BA control to be 98.99±10.56%, with partial control — 91.53±10.94%, with no control — 72.56±7.17%, $p<0.00001$. The correlation between ACQ-5 and FEV1 was –0.7, when $p<0.00001$.

The control level estimated by ACT-C showed the average values of FEV1 in patients with the achieved BA control to be 95.78±12.38%, with the lack of control — 85.99±17.08%; $p=0.0007$. The correlation between ACT-C and FEV1 was 0.37, when $p<0.00001$.

We assessed the intensity of bronchial responsiveness estimated by the tests with physical load or with bronchial spasmolytics (taking into consideration initial clinical status and spirometric findings) in 40 patients. As BA control level decreased, there was found the bronchial responsiveness rising. The correlation between ACQ-5 and the intensity of bronchial responsiveness was –0.55, when $p=0.0001$, that exceeded the correlation relationship between ACT-C and this parameter ($R=0.33$; $p=0.03$).

Conclusion. When diagnosing BA control level, one should take into consideration that spirometric parameters, as well as the intensity of bronchial responsiveness in the conditions of modern pharmacotherapy, demonstrate closer correlation with ACQ-5 indices compared to ACT-C.

Key words: bronchial asthma; spirometric parameters; bronchial responsiveness; ACQ-5; ACT-C.

At the present stage, the aim of treatment of bronchial asthma (BA) in children is gaining control over the symptoms and course of the disease, realized mainly during the basic anti-inflammatory therapy [1, 2]. Despite close attention of investigators to the problem, reliable and

comprehensive methods of diagnosing BA control level in individual patients are still absent. Partly, it is accounted for by different approaches to the definition of the very term “bronchial asthma control”, which is especially clearly seen in the selection of the time interval (period)

For contacts: Eliseeva Tatiyana Ivanovna, phone: +7 920-291-15-87; e-mail: eliseevati@yandex.ru

Table 1

Correlation (R, p) between the scale values of ACQ-5 and ACT/ACT-C in patients with BA and objective parameters (according to the literature published)

Tests	Patients	FEV1	BHR	FeNO	Literature
ACQ-5	Adults	p>0.05	p>0.05	p>0.05	[4]
ACQ-5	Adults	—	—	p>0.05	[5]
ACT	Adults	R=0.22	—	R=0.31	[6]
ACT-C	Children	p=0.003	—	p>0.05	[7]
ACT-C	Children	R=0.34; p=0.022	—	R=-0.51; p<0.001	[8]
ACT	Adults	R=0.18; p=0.025	—	R=-0.21; p=0.007	[9]
ACT	Adults	R=0.19; p<0.01	—	R=-0.16; p=0.01	[10]

Here: FEV1 is forced expiration volume in 1 s; BHR — bronchial hyperreactivity; FeNO — exhaled nitric oxide.

during which the control level of the illness is suggested to be assessed. In the latest guidelines of “An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations” the spread of time intervals for control level assessment varies from 1 week to 1 month [3].

Besides, BA currently is considered to be a heterogenic ailment, the basis of which is a combination of several pathogenetic processes. They are as follows:

A. Bronchial obstruction (edema of the bronchial mucous membrane, hyperproduction of sputum, spasm of the bronchial smooth muscles, formation of the inflammatory infiltrate in the bronchial walls). Diagnosing obstruction availability and intensity is presently carried on according to the clinical data and external respiration parameters, obtained spirometrically using “forced expiration” maneuver.

B. Bronchial hyperreactivity (changes of the bronchus caliber affected by various stimuli including cold air, allergens, strong odors, etc.). Diagnosis is based on history-taking and objective examination findings, alterations of spirometric parameters under provocation tests with bronchodilators and physical load, tests with bronchial spasmolytics.

C. Chronic allergic inflammation — a key pathogenetic process in BA, influencing the formation of both bronchial obstruction and bronchial hyperreactivity. Topical signs of eosinophilic inflammation (sputum, induced sputum), increase of nitric oxide content in the exhaled air, its metabolites in the exhaled air condensate and some others are taken into account in practical work in diagnosing the disease.

In recent years due to a complicated pathogenesis of asthma a complex approach to diagnosis of the disease control level is being developed, which must include the assessment of the following parameters:

1) clinical, including valid questionnaires for evaluation of the disease intensity and the character of its course (the most common of which are ACT-C, ACT, ACQ-5, being mainly different in the time interval of parameter assessment: ACT and ACT-C covering a month, ACQ-5 —

a week); the main drawback of them is the possibility of subjective assessment;

2) functional — evaluation of the airway patency and bronchial hyperreactivity using spirometry, and peakflowmetry; among the disadvantages is the need to perform forced expiration maneuver, which requires the cooperation of the patient and medical professional (a child can effectively fulfil spirometry when he is over 6);

3) inflammatory biomarkers — evaluation of the cellular composition of sputum and induced sputum, detection of nitric oxide metabolites in the exhaled air and in the condensate of the exhaled air, and other parameters; difficulty of finding a universal biomarker of inflammation in asthma is the chief drawback, as inflammation in asthma may have some phenotypical features (predominantly eosinophilic, predominantly neutrophilic). The content of various biomarkers depends not only on the inflammation intensity, but also on the prevailing phenotypic inflammation mechanism in an individual patient.

None of the above approaches is universal, and correlation between separate objective parameters and control level, which are differently evaluated by specialists, is often not reliable, which is reflected by the results of scanty investigations (Table 1).

Thus, data on associative relations of BA control level, evaluated by ACQ-5 and ACT-C (ACT) scales, and parameters of objective examinations of the patients with BA are rather controversial. Investigations comparing correlation of the data of the two questionnaires and objective parameters, carried out in the same patient group, are absent. In this connection, comparison of correlation of the test findings of clinical evaluation of BA control level and objective parameters of control level, primarily functional, is believed to be of considerable value.

The aim of the investigation was to assess the relationship of ACQ-5 and ACT-C indices and spirometric parameters in children with bronchial asthma, reveal confidential intervals of these parameters typical for different levels of bronchial asthma control, determined according to these questionnaires.

Materials and Methods. 130 patients aged from 5 to 11 years mainly with atopic BA and different control levels of the disease have been examined. All children underwent treatment according to the stage of the illness and its severity following standard recommendations [2]. Of them 25 children with intermittent, mainly, pollen BA were not given basic therapy at the time of investigation (they were provided with allergen-specific immunotherapy by causative allergens), however antihistaminic preparations of the last generation were used in the treatment complex. 45 patients were taking Singulair in the doses pertaining to their age, 36 — combined medications of inhaled corticosteroid and long term β_2 -agonist (Seretide — 24, Symbicort — 12). 24 more children were undergoing complex therapy due to exacerbation including inhalations of short-term β_2 -antagonists via nebulizer.

Standard clinical, allergological, immunological and functional examination was performed for all patients,

as well as testing to determine BA control level using the scales of Asthma control questionnaire — 5 (ACQ-5) [11] (Dept of Clinical Epidemiology and Biostatistics, McMaster University Faculty of Health Sciences, Hamilton, Ontario, Canada) and Childhood Asthma control test (ACT-C) [12] (National Jewish Medical and Research Center and the University of Colorado School of Medicine, Denver, USA).

Spirographic investigations were carried out using Master-Screen Pneumo (Jaeger, Germany). Parameters were assessed by comparison with a standard norm [13].

Bronchial hyperreactivity (BHR) was studied by the tests with physical load (pedaling veloergometer Kettler AX1, (Germany) with a speed 60 rev./min. and a load 1W/kg of the body weight for 5 min). Dynamics of spirographic values at the fifth minute after the load was compared with that of the preload ones. Exercise tests were used in children whose reference spirogram values were within accepted norm [14]. When reference spirogram parameters reduced below the norm, as well as in children treated for exacerbation of the disease, BHR determination in the loading test was not conducted. In these patients tests on reversibility of bronchial obstruction with bronchial spasmolytics (inhalation of 200 µg of salbutamol — a dosed aerosol — via a spacer) was performed: reference spirographic parameters were compared with the values of spirogram, recorded in 20 minutes after the broncholytics inhalation. Changes of spirographic parameters were evaluated by the formula $(A-B)/B$ (%), where B — reference values of spirographic parameter, A — parameter value after the test with a physical load or broncholytic.

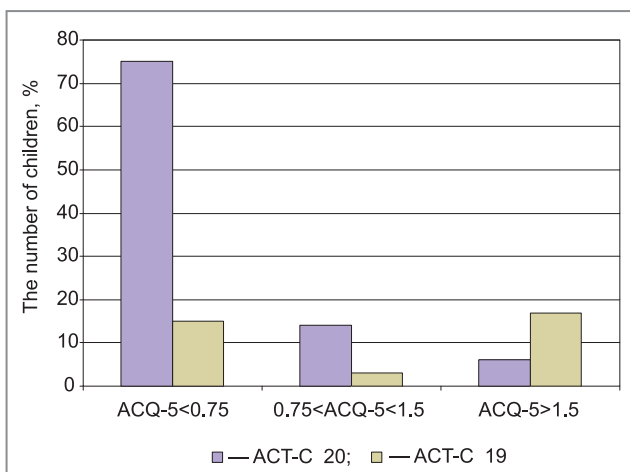
In statistical analysis changes of FEV1 caused by the abovementioned stimuli (physical exercise, broncholytics) were processed in one data array, changes in FEV1 under the influence of broncholytics being taken with a sign opposite to that of the obtained result (multiplied by -1).

Data are presented in the form of $M \pm CD$, where M is mean, CD — standard deviation. Program Package Statgraphics plus was used for statistical analysis.

Results and Discussion. According to the assessment data of ACQ-5 test in 90 children at the time of examination full control of the disease symptoms was noted (ACQ-5 <0.75 scores, mean value of the test 0.23 ± 0.25 scores). In 17 partial control was diagnosed (ACQ-5 ranged from 0.75 to 1.5 scores, mean value 0.89 ± 0.16 scores), while in 23 BA control was absent (ACQ-5 more than 1.5 scores, mean value 2.62 ± 0.93 scores). While assessing the same children by ACT-C test the controlled BA course (ACT-C ≥ 20 scores) was noted in 95 children, lack of control (ACT-C ≤ 19) in 35 patients. Correlation between the two given tests was -0.62 , when $p < 0.00001$.

Comparison of BA control level assessments using the two tests (ACQ-5 and ACT-C) is shown in Fig.1.

Of 90 children with achieved disease control, diagnosed with the help of ACQ-5 test, BA course considered as controlled in ACTC-test was assessed in 75 children, and in 15 patients ACT-C test results showed no disease control. Among 17 children with partial symptom control level (according to ACQ-5 test), BA controlled course by ACT-C test was diagnosed in 14 patients, absence of



Comparison of BA control level assessments using ACQ-5 and ACT-C

control — in 3 children. Of 23 patients with no BA symptom control, judging by ACQ-5 scale, the course of the disease was assessed as controlled by ACT-C test in 6 patients, the absence of control was diagnosed in 17.

If we combine the groups of patients with partial control and no symptom control according to ACQ-5 test, coincidence of BA control level assessments by ACQ-5 and ACT-C tests occurred in 73% of patients (95 of 130), noncoincidence was in 27% of patients (35 of 130).

Mean values of FEV1 in patients with complete control of BA symptoms, assessed by ACQ-5 test, amounted to $98.99 \pm 10.56\%$, in patients with partial control 91.53 ± 10.94 , in patients with no control they were $72.56 \pm 7.17\%$ of the standard figures. Differences between the groups are statistically significant, $F=50.22$; $p < 0.00001$. Coefficient of correlation in the studies of ACQ-5 and FEV1 value relationship is rather high and made -0.70 ($F=92.7$; $p < 0.00001$) in this sample. Similar statistics of FEV1 in children with various BA control level determined by ACQ-5 and ACT-C tests is presented in Tables 2 and 3.

Assessment of control level according to ACT-C test gave mean values of 95.78 ± 12.38 for FEV1 in patients with achieved control, with no control — $85.99 \pm 17.08\%$ of the standard norm. Differences between the groups are statistically significant, $t=11.96$; $p=0.0007$. Coefficient of correlation in the study of the relationship of ACT-C test values and those of FEV1 in this sample was 0.37 ($F=20.34$; $p=0.0000$). Correlation between ACT-C and FEV1 test values in this investigation is close to the findings obtained in the studies of G.L. Piacentini et al. [8].

Thus, revealed correlation between FEV1 and ACQ-5 scale values is significantly more pronounced than between FEV1 and ACT-C test values. Considering the fact that ACQ-5 shows the intensity of disease symptoms covering a week interval, while ACT-C — a month period, changes of FEV1 in children asthma are believed to be sufficiently dynamic.

In 40 patients the intensity evaluation of BHR was made. It was estimated by the tests with physical load or with bronchial spasmolytics (taking into account initial clinical

Table 2

Statistical data on FEV1 level (% of the standard norm) in children with various asthma control level, assessed by ACQ-5 scale

Values	ACQ-5<0,75	0,75<ACQ-5<1,5	ACQ-5>1,5
Mean	98.99	89.31	70.25
SD	10.56	10.86	14.04
Median	99.0	90.0	72.27
Minimum–Maximum	80.00–121.10	76.00–107.00	34.00–93.29
95% CI	96.86–101.12	84.36–94.25	65.58–75.91

Here: SD is standard deviation; CI — confidential interval.

Table 3

Statistical data on FEV1 level (% of the standard norm) in children with various asthma control level, estimated by ACT-C scale

Values	ACT-C≥20	ACT-C≤19
Mean	96.05	84.75
SD	12.39	18.27
Median	98.0	82.70
Minimum–Maximum	61.00–121.10	34.00–117.51
95% CI	93.57–98.54	78.47–91.02

Table 4

The effect of tests with physical load and broncholytics (with a reversed sign) on FEV1 changes taking into account ACQ-5 and ACT-C scale values

The values of tests	Change FEV1, %	Statistics
ACQ-5<0.75	-6.77±6.93	F=4.55
0.75<ACQ-5<1.5	-10.57±9.09	p=0.017
ACQ-5<1.5	-18.67±13.69	
ACT-C≥20	-6.88 ± 6.74	F=6.05
ACT-C≤19	-14.27±12.07	p=0.02

status and spirogram findings). The obtained results (Table 4) demonstrate the growth of BHR with the decrease of BA control characteristics. The data are comparable in the assessment of the control level using both ACQ-5 and ACT-C tests, BHR in patients with the achieved BA control not exceeding 10%, which is actually a variant of norm. When control is absent, mean values of BHR are observed to run beyond the permissible ones, no matter what assessment method was used.

Coefficient of correlation of ACQ-5 test values and BHR intensity was -0.55 with p=0.0001, which exceeds correlation between ACT-C values and BHR parameters, the coefficient of correlation between which was 0.33 with p=0.03.

Thus, in diagnosing BA control level in children it should be taken into consideration that spirometric parameters, as well as BHR intensity in the condition of modern pharmacotherapy demonstrate much closer correlation with ACQ-5 test values than with ACT-C test. This, probably reflects relatively rapid dynamics of functional parameters in children with BA and shows that functional methods may be used with a high degree of confidence for making

objective evaluation of the patient's condition in a relatively "short-term" perspective (weeks)

95% confidence intervals for FEV1 typical for the level of complete BA symptom control make 96.89–101.12%, for the level of partial control they are 84.36–94.25%, for no control 65.58–75.91% (control level assessed by ACQ-5 test). Data of the confidence intervals may be applied in practice for additional objective evaluation of the current control level of bronchial asthma in children.

Conclusion. Statistically significant correlation between FEV1 and values of the tests used for diagnosing the level of disease control are established in children with asthma. In this case the correlation relationship between FEV1 and ACQ-5 scale values, showing the intensity of disease symptoms during a week preceding questioning, surpasses the correlation between FEV1 and values of ACT-C test reflecting specific clinical signs of BA during a month before questioning. Intensity of FEV1 changes under the influence of different stimuli (physical exercises and broncholytics) also has more significant associative relations with the values of ACQ-5 test than with the findings of ACT-C test.

The dynamics of changes of spirometric parameters, as well as the values of the tests with physical load and the tests on reversibility of bronchial obstruction with broncholytics gives the advantage in diagnosing relatively short-term processes (closer to a week) in children. Making objective assessment for long-term processes (closer to a month) requires, probably, searching for additional diagnostic methods.

References

- GINA (Global strategy for asthma management and prevention). Updated 2011. http://www.ginasthma.org/uploads/users/files/GINA_Report_2011.pdf
- Volkov I.K., Geppe N.A., Kondyurina E.G., Korostovtsev D.S., et al. *Natsional'naya programma "Bronkhial'naya astma u detey. Strategiya lecheniya i profilaktika"* [National program "Bronchial asthma in children. Management strategy and prevention"]. Moscow: Original-maket; 2012; 184 p.
- Reddel H.K., Taylor D.R., Bateman E.D., et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations. Standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180(1): 59–99.
- Sazlidere H., Celikel S., Inönü H., Doruk S., et al. The relation between nitric oxide levels in exhaled breath condensate and asthma control questionnaires in asthma patients. *Tuberk Toraks* 2010; 58(1): 5–15.
- Lopes C., Fonseca J., Delgado L., Moreira A., Barros R., Moreira P., Castelo-Branco Mda G. Assessing asthma control: questionnaires and exhaled nitric oxide provide complementary information. *Eur Respir J* 2008; 32(5): 1419–20.
- Shirai T., Furuhashi K., Suda T., Chida K. Relationship of the asthma control test with pulmonary function and exhaled nitric oxide. *Ann Allergy Asthma Immunol* 2008; 101(6): 608–613.
- Waibel V., Ulmer H., Horak E. Assessing asthma control: symptom scores, GINA levels of asthma control, lung function, and exhaled nitric oxide. *Pediatr Pulmonol* 2012; 47(2): 113–118.
- Piacentini G.L., Peroni D.G., Bodini A., Bonafiglia E., et al. Childhood Asthma Control Test and airway inflammation evaluation in asthmatic children. *Allergy* 2009; 64(12): 1753–1757.
- Papakosta D., Latsios D., Manika K., Porpodis K. Asthma Control Test is correlated to FEV1 and nitric oxide in Greek asthmatic patients: influence of treatment. *J Asthma* 2011; 48(9): 901–906.

10. Alvarez-Gutiérrez F.J., Medina-Gallardo J.F., Pérez-Navarro P., Martín-Villasclaras J.J., et al. Comparison of the Asthma Control Test (ACT) with lung function, levels of exhaled nitric oxide and control according to the Global Initiative for Asthma (GINA). *Arch Bronconeumol* 2010; 46(7): 370–377.

11. Juniper E.F., Gruffydd-Jones K., Ward S., Svensson K. Asthma control questionnaire in children validation, measurement properties, interpretation. *Eur Respir J* 2010; 36: 1410–1416.

12. Liu A.H., Zeiger R.S., Sorkness C., Mahr T., et al. Development

and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007; 119(4): 817–825.

13. Shiryayeva I.S., Lukina O.F., Reutova B.C., et al. *Funktsional'nye metody issledovaniya bronkhial'noy prokhodimosti u detey* [Functional diagnostic techniques of bronchial patency in children]. Moscow: MZ SSSR; 1990.

14. Silverman M., Anderson S.D., Andrea T. Standardization of exercise tests in asthmatic children. *Arch Dis Child* 1972; 47(256): 882–889.