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PHENOTYPE-ORIENTED TREATMENT OF BRONCHIAL ASTHMA IN CHILDREN DEPENDING ON THE TERM OF ONSET OF THE DISEASE

Olena Koloskova[1], Lorina Ivanova[2], Tetiana Bilous[3], Nataliia Shevchenko[4], Maryana Dikal[5], Tamara Kopchuk[6]

[1] PhD, MD, Professor, Department of Paediatrics and Children Infectious Diseases, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine, Teatralna sq., 2, Chernivtsi, 58002

[2] PhD, MD, Professor, Department of Paediatrics and Children Infectious Diseases, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine, Teatralna sq., 2, Chernivtsi, 58002, Ukraine

[3] PhD, Associate Professor, Department of Paediatrics and Children Infectious Diseases, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine, Teatralna sq., 2, Chernivtsi, 58002

[3] Department of Paediatrics and Children Infectious Diseases, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Teatralna sq., 2, Chernivtsi, 58002

[4] Aspirant, Department of Paediatrics and Children Infectious Diseases, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine, Teatralna sq., 2, Chernivtsi, 58002

[5] PhD, Associate Professor, Department of Bioorganic and Biological Chemistry and Clinical Biochemistry, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine, Teatralna sq., 2, Chernivtsi, 58002

[6] PhD, Associate Professor, Department of Pharmacology, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine, Teatralna sq., 2, Chernivtsi, 58002

Abstract:

Objectives: To determine and analyze the efficacy of rapidly relieving therapy during exacerbations and basic anti-inflammatory treatment in the period of bronchial asthma remission in school children with alternative phenotypes of the disease by the time of its onset.

Methods: Keeping to the principles of bioethics a comprehensive retrospective examination of 50 school children suffering from bronchial asthma was performed. The patients were divided into two clinical groups depending on the term of the onset of the disease. The first (I) clinical group included 25 children with the early onset phenotype of bronchial asthma (under 3 years of age), and the second (II) group (comparison) included 25 patients with bronchial asthma of a late onset (older than 6-years of age).

Results: Inconsiderably pronounced syndrome of bronchial obstruct ion during admission regarding exacerbation of bronchial asthma was found to occur in patients with bronchial asthma phenotype of a late onset (12,1 against 11,7 points, P>0,05). Although, since the third day severity of obstruction of the respiratory tract prevailed in the group of children with the phenotype of an early onset. In case of the early onset phenotype daily symptoms of bronchial asthma occurred four times as much, and night ones – twice as much as compared to the patients of the II clinical group.

Corresponding author: Olena Koloskova

Conclusion: While indicating releiving therapy regarding exacerbation of bronchial asthma on admission the patients with the early onset phenotype of bronchial asthma should be recommended to take more aggressive symptomatic therapy since the first day of hospitalization; and children with the first onset of the disease after the age of six higher doses of rapidly releiving drugs should be recommended in the first three days of treatment, and the volume of therapy should be reviewed more often.
Key words: children, asthma, onset of the disease.

INTRODUCTION

In spite of clear domestic and international standards and protocols of treatment of bronchial asthma (BA) introduced into practice, in 10-30% of cases the basic anti-relapsing therapy including different groups of drugs possessing anti-inflammatory effect fails. Nowadays resistance to the standard anti-inflammatory therapy is associated with phenotype polymorphism of BA. Its occurrence is considerably promoted by both environmental factors and genetic predisposition to the development of this pathology [1].

Persisting wheezing-syndrome of an early age, as it is indicated [2], is heterogeneous in its structure, in 55,4% of cases it is of an episode and self-limiting character, in 15,9% of cases it becomes transient by its phenotype ceasing at the pre-school age, in 19,7% of children it persists till 15 years of age, and in 9% of patients it advances to the adult period of life. The uncertainty to prognosticate relapses of bronchial obstruction syndrome at the early age is partially a cause of untimely administration of anti-inflammatory therapy for children. Moreover, according to contemporary evidence of epidemiological investigations and international regulating documents (Global Initiative for Asthma (GINA, 2011), valid diagnostic criteria to verify BA in children of an early age have not been elaborated yet. Contemporary diagnostics of the disease is based only on clinical signs: frequent «wheezing» (more than once a month); cough or sibilant rale associated with activity of a child; night cough not associated with acute respiratory viral disease (ARVD); absent seasonal pattern of «wheezing» and retention of symptoms till 3 years of age. All of them are indicative of a high probability of BA in children [3-5].

All the mentioned above promotes difficulties in verification of the diagnosis of BA and untimely administration of basic drugs. At the same time, nowadays certain data are accumulated emphasizing the importance of timely initiation of anti-inflammatory therapy to achieve the control over the disease. Thus, a study carried out in real-time operation mode showed that under conditions of delayed planned basic anti-inflammatory treatment of asthma in children in 5 years the function of the lungs, the need in anti-inflammatory drugs and asthma control become reliably worse than those with timely initiated treatment [6].

Therefore, considering alternative BA phenotypes by the time of onset (verification proper) of the disease of an early and late onset, both clinical-paraclinical differences and differences in response to regulated standard anti-inflammatory and rapidly relieving therapy can be found. This oriented approach to different periods of onset of the disease could promote personal standard therapeutic tactics in children with the mentioned phenotypes of BA, although now it has not been elaborated in the scientific literature available.

MATERIALS AND METHODS

Keeping to the principles of bioethics a comprehensive retrospective examination of 50 school children suffering from BA was performed. The patients were divided into two clinical groups depending on the term of the onset of the disease. The first (I) clinical group included 25 children with the early onset phenotype of BA (EOP – under 3 years of age), and the second (II) group (comparison) included 25 patients with BA of a late onset (LOP – older than 6-years of age). The clinical groups were comparable by the main clinical characteristics. Thus, I clinical group included 18 boys (72,0%) and 7 girls (28,0%). II group of comparison included 20 boys (80,0%, $P\varphi>0,05$) and 5 girls (20,0%, $P\varphi>0,05$). An average age of patients in the main group was 11,4±3,3 years, and school children with LOP –

12,7±3,3 years (P>0,05). 8 children of I group (32,0%) were urban residents and 17 patients (68,0%) – rural ones. The group of patients with LOP included 11 individuals (44,0%), residing in towns, and 14 patients (56,0%, Pφ>0,05) were rural inhabitants. According to the degree of severity in I group mild form of the disease was not detected, 6 children had moderate form (24,0±17,4%), and severe asthma was determined in 19 children (76,0±9,7%). In the group of comparison one child was diagnosed with mild form of the disease, moderate and severe asthma was registered in 7 (28,0±16,9%, P>0,05) and 17 (68,0±11,6%, P>0,05) patients respectively, which did not conform with the evidence found in literature indicating that BA with late onset is characterized by more severe and persisting course [7]. According to our findings inconsiderably more severe course of the disease was found in patients with EOP which could be explained by delayed onset of basic treatment in a part of the patients since the period of infancy in the period of early childhood.

The diagnosis of BA and its management were made according to "The Uniform Clinical Protocol of Primary, Secondary (Specialized) Medical Aid "Bronchial Asthma in Children" (the Order of the Ministry of Public Health of Ukraine №868 (enclosure 2,3) dated October 8, 2013. BA control was assessed by means of a score questionnaire at the beginning and at the end of the prescribed course of anti-inflammatory basic therapy. The questionnaire included clinical signs of BA presented in points assessed by patients and their parents, as well as the scale of instrumental examinations [8-10], filled in by an analyst by spirography findings. Ten and less points enabled to identify controlled BA, 11-16 points were associated with partial control of the symptoms of the disease, and higher than 17 points – uncontrolled variant of BA.

Clinical peculiarities of an attack were examined by means of constellation scale of bronchial obstruction syndrome severity. Therefore, assessment of severity of BA attacks was formalized, and thus, the more severe bronchial obstruction syndrome was, the higher total score was detected.

The parameters of clinical-epidemiological risk of the event and efficacy of treatment of patients were assessed from the positions of clinical epidemiology: probability of realization was determined considering probable values of the relative risk (RR), attributive risk (AR) and odds ratio (OR) with detection of their confidential intervals (95% CI). Efficacy of the treatment conducted was assesses considering absolute risk decrease (ARD) and relative risk decrease (RRD) of an unwanted event taking into account a minimum number of patients (MNP) requiring treatment to achieve 1 positive result [11].

RESULTS

The research demonstrated that during attacks of BA β_2-agonists of quick action in the groups of comparison were administered in 96% of patients, systemic glucocorticosteroids (sGCS) – in 76,0% of cases in I clinical group and in 62,0% of examinations among children with late onset of the disease (P_φ>0,05), and inhalation glucocorticosteroids (iGCS) – in 12,0% and 8,0% of patients of I and II groups respectively. Disorders of the water-salt metabolism were corrected by means of a short course of infusion therapy in 44,0% and 36,0% school children of comparison groups respectively (P_φ>0,05).

The absence of reliable differences between the frequency of administration of certain releiving drugs in the groups of comparison stipulated the necessity of a dynamic detection of their efficacy by the expressiveness of clinical symptoms in children with alternative phenotypes of BA onset (Fig. I).

Fig. I. Score assessment of bronchial obstruction severity during bronchial asthma attack in children of comparison groups

Therefore, on admission regarding exacerbation of BA inconsiderably less pronounced bronchial obstruction syndrome was found in patients with late onset phenotype of BA (12,1 against 11,7 points, P>0,05), although since the third day the severity of obstruction of the respiratory tract prevailed in the group of children with EOP. Attributive risk of more severe course of BA attack in children with LOP concerning the patients with manifested symptoms of the disease to six years was 11,0%, RR - 1,25 (95% CI: 0,64-

2,42) and OR - 1,56 (95% CI: 0,42-5,82).
In the dynamics of observation beginning with the third day of rapidly relieving therapy the indices of reduced risk of more pronounced obstruction of the respiratory tract in patients of II clinical group as compared to the patients with EOP were studied (Table).

Table

Dynamic analysis of efficacy of relieving treatment of asthma attack in children with late onset phenotype

To assess the efficacy of the phenotype-oriented basic treatment of BA the anamnesis of the disease of patients from the clinical groups of comparison was carried out, which demonstrated that in spite of indicated basic therapy during three late months, children developed exacerbations requiring hospitalization into a specialized department. A part of patients suffering from BA with exacerbations was 1,8 times less among the patients with EOP and was 32,0±9,3% cases, and among school children with LOP – 56,0±9,9% cases (P_{φ}>0,05). AR of the control loss over BA and occurring exacerbations in the representatives of II group concerning patients with EOP was 24,0%, RR – 1,54 (95% CI: 0,82-2,90) with OR – 2,70 (95% CI: 0,85-8,57). Thus, the patients with manifestation of BA symptoms after the age of six years were characterized by 2,7 times higher risk of hospitalization concerning exacerbations of the disease.

The frequency of the main symptoms of BA during three months in patients of the groups of comparison is presented in Fig. II.

Fig. II. Control over the symptoms of bronchial asthma in patients of I and II clinical groups (% of patients). Note. * – P < 0,05 between the groups of comparison

Therefore, with EOP daily symptoms of BA occurred 4 times as frequent and night symptoms – twice as frequent in comparison with the patients from II clinical groups. Thus, AR of more than one episode of daily symptoms during a week among the school children of I clinical group concerning the patients with symptoms manifested after six years of age was 28,0%, RR -1,44 (95% CI: 0,40-5,17) and OR - 6,47 (95% CI: 1,23-34,01). In case of EOP a higher risk of frequent night symptoms of BA occurred: AR – 12,0%; RR – 1,16 (95% CI: 0,44-3,04) and OR – 2,32 (95% CI: 0,51-10,54).

According to a worse control over BA symptoms among the representatives of I group the risk of situational use of rapidly acting β_2-agonists increased: AR –20,0%; RR – 1,63 (95% CI: 0,94-2,81) and OR – 2,30 (95% CI: 0,73-7,27). Therefore, the patients with early onset phenotype of BA have the risk of a worse control over asthma symptoms, in particular, the chances of more frequent daily episodes were 6,5 times as much, night symptoms and situational use of bronchodilators – 2,3 times a s much. Although by the frequency of restriction of physical activity there was no difference found in the groups of comparison.

Clinical peculiarities of BA found with alternative phenotype onset on one hand could be explained by delayed start of anti-inflammatory basic therapy at early age of patients from I group, and on the other hand – by the formation of irreversible changes in the respiratory tract in the process of a long insufficiently controlled inflammatory process – possible remodeling [12]. The latter point can be evidenced by the obtained correlations among the patients with EOP. The frequency of daily symptoms reliably correlated with duration of the disease (r=0,46, p<0,05), and the number of night symptoms had a direct interrelation with complicated allergic anamnesis (r=0,55, p<0,02). On the contrary, among school children suffering from BA with LOP a reliable interrelation between the frequency of characteristic symptoms and the place of residence was found. Thus, residing in rural area correlated with higher frequency of daily (r=0,72, p<0,01), night symptoms (r=0,53, p<0,05), administration of symptomatic therapy in the form of rapidly acting β_2-adrenergic agonists (r=0,45, p<0,05) and restriction of physical activity (r=0,63, p<0,01).

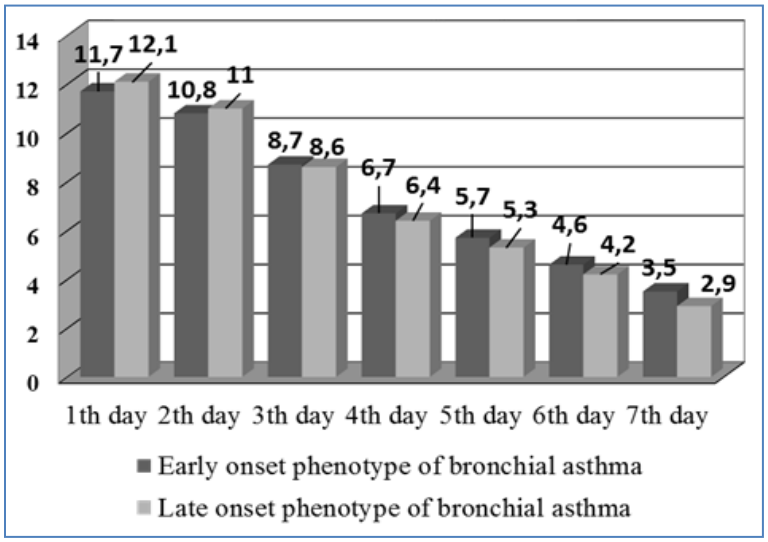

Figure 1: Score assessment of bronchial obstruction severity during bronchial asthma attack in children of comparison groups

Table 1: Dynamic analysis of efficacy of relieving treatment of asthma attack in children with late onset phenotype

Days of in-patient treatment	Absolute risk decrease, %	Relative risk decrease of an unwanted event, % (95% CI)	Minimum number of patients requiring treatment to achieve 1 positive result, (95% CI)
Third	5,9	11,1 (5,7-19,0)	9,0 (4,1-16,5)
Fourth	52,9	56,2 (45,9-66,2)	1,8 (0,1-6,9)
Fifth	5,9	11,1 (5,7-19,0)	9,0 (4,1-16,5)
Sixth	41,2	58,3 (48,0-68,1)	1,7 (0,1-6,8)
Seventh	17,6	30,0 (21,2-40,0)	3,3 (0,7-9,2)

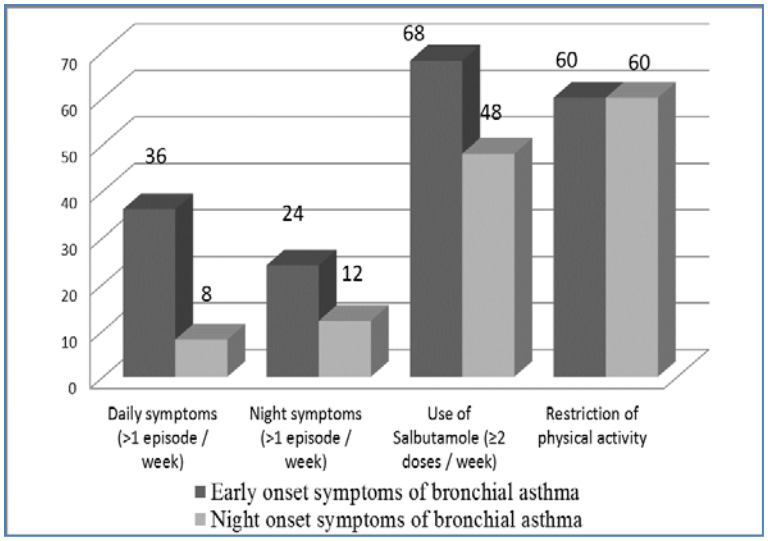

Figure 2: Control over the symptoms of bronchial asthma in patients of I and II clinical groups (% of patients). Note. * – P < 0,05 between the groups of comparison

DISCUSSION

The data presented emphasize ghe highest efficacy of rapidly relieving desobstructive therapy of BA exacerbation in patients with LOP asthma concerning children suffering from BA of an early onset of the disease. The study showed that patients with LOP contrary to children with early onset of the disease were hospitalized with more severe course of BA attack, although since the third day of treatment the rates of bronchial desobstruction were quicker against the ground of adequate releiving therapy. Summing up the data obtained it should be noted that treatment of BA attacks conforms with domestic and international recommendations, and irrespective of the phenotype of the disease the main medical means used for arresting the symptoms of exacerbation are symptomatic bronchodilatory drugs and glucocorticosteroids [1, 8]. So the analysis of the obtained results showed that children suffering from BA irrespective of the onset of the disease are recommended to take basic ascending therapy, that is, anti-inflammatory therapy should be indicated in higher doses (first of all – inhalation glucocorticosteroids).

In case of EOP considering longer duration of the disease a long (no less than three months) anti-relapsing treatment after the latter exacerbation with correction of the dose of anti-inflammatory drugs every month is reasonable. In children with increased atopic reactivity found more frequently in case of EOP of BA specific allergic vaccination concerning the main trigger allergens should be carried out. In case of frequent night symptoms of the disease more frequently found in children with early onset of BA prolonged theophyllines are recommended to be added to the complex of anti-relapsing treatment. They do not only intensify the action of glucocorticosteroids but inhibit the activity of neutrophils which are the main effector cells of night episodes of bronchial obstruction [13].

On the contrary, among children suffering from BA with late onset phenotype, especially those residing in rural area, more careful explanatory work should be performed concerning the peculiarities of the course and treatment of this pathology; and a cycle of training should be recommended at “Asthma-school”.

CONCLUSIONS

1. While indicating releiving therapy regarding exacerbation of bronchial asthma on admission the patients with EOP should be recommended to take more aggressive symptomatic therapy since the first day of hospitalization; and children with the first onset of the disease after the age of six higher doses of rapidly releiving drugs should be recommended in the first three days of treatment, and the volume of therapy should be reviewed more often.
2. Since among the patients with EOP in the period between attacks the frequency of daily and night symptoms of the disease prevails which is reliably correlated with duration of the disease itself, such patients should take basic treatment oposite to relapsing treatment according to the «step up» principle.
3. Since the patients with LOP have in 2,7 times higher risk of hospitalization concerning exacerbation of the disease and the symptoms of poor control are associated with residing in rural area, it can be indirectly indicative of violation of therapeutic regimen by patients and requires more intensive educational-explanatory work with such a contingent of patients.

REFERENCES

1. Holgate ST, Davies DE, Powell RM, Howarth PH, Haitchi HM, Holloway JW. Local genetic and environmental factors in asthma disease pathogenesis: chronicity and persistent mechanisms. Eur. Respir J. 2007; 29: 793- 803. PMID: 17400878, DOI: 10.1183/09031936.00087506
2. Middleton's Allergy: Principles and Practice. Adkinson NF, Bochner BS, Burks W, Busse WW, Holgate ST. Elsevier Health Sciences, 2013. - 1896 p.
3. Ober C, Hoffman S. Asthma genetics 2006: the long and winding road to gene discovery. Genes and Immune. 2006; 7 (2): 95-100. PMID: 16395390, DOI: 10.1038/sj.gene.6364284
4. Holt PG, Sly PD. Interactions between respiratory tract infection and atopy in the

aetiology of asthma. Eur. Respir. J. 2002; 19: 538-545. PMID: 11936536, DOI: 10.1183/09031936.02.00229302

5. Asher MI. Urbanization, asthma and allergies. Thorax. 2011; 66 (12): 1025-1026. PMID: 21948729, PMCID: PMC3221320, DOI: 10.1136/thoraxjnl-2011-201019
6. Selroos O, Lofroos AB, Pietinalho A, Riska H. Asthma control and steroid doses 5 years after early or delayed introduction of inhaled corticosteroids in asthma: a real-life study. Respiratory Medicine. 2004; 98: 254–262. https://doi.org/10.1016/j.rmed.2003.10.007
7. Kapitein B, Hoekstra MO, Nijhuis ENJ, Hijnen DJ, Arets HG, Kimpen JL et al. Gene expression in CD4+ T–cells reflects heterogeneity in infant wheezing phenotypes. Eur. Respir. J. 2008; 32: 1203-1212. PMID: 18614563, DOI: 10.1183/09031936.00020108
8. Boulet L-P., Boulet V., Milot J. How should we quantify asthma control?: a proposal. Chest. 2002; 122: 2217-2223. PMID: 12475866
9. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE et al. Stinging insect hypersensitivity: a practice parameter update 2011. J Allergy Clin Immunol. 2011 Apr;127(4):852-4.e1-23. doi: 10.1016/j.jaci.2011.01.025.
10. Juniper EF, O'Byrne PM, Ferrie PJ. Measuring Asthma Control. Clinic Questionnaire or Daily Diary? Am. J. Crit Care Med. 2000; 162: 1330-1334.
11. Medical Epidemiology / RS. Greenberg, SR. Dansels, WD. Flenders [et al.]. – [4th Edition]. – Norwalk, CT: Appleton&Lange, 2004. – 196 p.
12. Rossi GA. Airway remodeling: structure and physiology. Pediatr Pulmonol Suppl. 2004; 26: 100-102.
13. Hansel, T.T., Tennant, R.C., Tan, A.J., Higgins, L.A., Neighbour, H., Erin, E.M., Barnes, P.J. Theophylline: Mechanism of action and use in asthma and chronic obstructive pulmonary disease. Drugs of today, 2004, 40(1):55-69. DOI: 10.1358/dot.2004.40.1.799438