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CHANGES IN CHOLINERGIC AND ADRENERGIC REGULATIONS OF BRONCHIAL AND BILIARY WAYS TONES IN A COMBINED COURSE OF BRONCHIAL ASTHMA AND CHRONIC CHOLECYSTITIS

Key words: *bronchial asthma, chronic acalculous cholecystitis, adrenergic and cholinergic regulation, acetylcholinesterase.*

Abstract. *The paper presents data from a study of the neuroendocrine regulation of nonstriated muscles, bronchial tree and the gallbladder tones by means of an assessment of the adrenergic and cholinergic systems state in patients, suffering from bronchial asthma and chronic acalculous cholecystitis. Adrenergic and cholinergic activities as well as cortisol secretion have significantly changed.*

Introduction

Bronchial asthma (BA) is a global problem in the internal medicine, leading among respiratory diseases; therefore it remains an actual problem for a scientific research both in Ukraine and around the world [1, 6, 7]. Unfavorable epidemiologic situation, severe, uncontrolled course of BA are caused by lack of timely detection of sick people when the signs are not significant, by such factors as allergens, xenobiotics, chronic nidi of viral and bacterial infection, parasitic invasions, use of enzymatic domestic chemicals, uncontrolled use of a great variety of drugs, active and passive cigarette smoking as well as stresses [6, 8].

According to data of different authors, a combined course of BA and diseases of digestive organs occurs in 8-50% of cases, and gastrointestinal diseases occur combined with atopic BA twice as often as with infection-dependant BA [3].

Different authors describe the development of gastric ulcer, gastric and duodenal erosions, chronic gastritis, duodenitis, reflux esophagitis and sliding hiatal hernia, duodenogastric reflux, changes in the liver, inflammation of the biliary tract and pancreas in the patients with chronic inflammatory diseases of the lungs and bronchi [2, 4]. Chronic acalculous cholecystitis (CAC) combined with BA, according to some authors, is known for the prevalence of aseptic inflammation in the gallbladder (GB), interrelation of exacerbations with BA exacerbation, more torpid, compared to BA, and atypical course with less intensive pain syndrome, prevalence of dyskinetic phenomena over the inflammatory ones with formation of hypokinetic dyskinesias of the GB [3, 4]. With hypokinetic dyskinesias of the GB and a basis therapy of BA, amplification of CAC is predominant [5]. Using basic therapy and в-adrenoceptor agonists as well as cholinergic antagonists contribute to GB hypokinetic dyskinesias intensification [4, 9].

Objective

To study the features of adrenergic and cholinergic regulations of bronchial tone and that of the gallbladder in patients with combined course of chronic acalculous cholecystitis and bronchial asthma.

Material and methods

92 patients were involved in the study: 30 patients with mild and moderate persisting BA (1st group), 30 patients with mild and moderate persisting BA of comorbid CAC in the acute phase (2nd group), 32 patients with CAC in the acute phase (3rd group) and a control group - 30 practically healthy individuals (PHI) of the respective age.

Ventilation lung function was studied by means of a computer Spirograph «Pneumoscope» company «Jaeger» (Germany), «Spirosift 3000» company «Fukuda Denshi» (Japan). The degree of disturbance in the respiratory function was evaluated through an analysis of spirography findings and a curve «flow-volume» by comparing the findings obtained with the appropriate parameters for a given age, sex, height and weight before and after pharmacological tests with salbutamol. The range of normative parameters was considered 80-120% of appropriate. Ultrasonographic testing of the liver, the GB, and the pancreas was carried out in 100% of patients by means of an ultrasound scanner «Au-4 Idea» (Biomedica, Italy). The catecholamine depositing function of erythrocytes (CDE) was studied according to the H.I. Mardar's and D.P. Kladienko's method. The cholinergic system tone was assessed by the activity of acetylcholinesterase (AChE) in the blood serum.

Results and discussion

All the patients with BA and BA combined with CAC had a marked predominance of the

parasympathetic nervous system, as evidenced by the established significant decrease of CDE (Table 1) in patients with isolated asthma is 1.4 times ($p < 0.05$), in patients with asthma combined with CAC - there was more intense inhibition of enzyme activity – in 1.8 times ($p < 0.05$) and in patients with CAC of the 3rd group there were identical changes – a decreased activity of CDE in 1.6 times ($p < 0.05$) with significant intergroup differences between the groups ($p < 0.05$).

These data suggest, that patients, suffering from asthma combined with CAC, have a cholinergic imbalance due to, vagotonia, established on clinical grounds, and also due to AChE activity inhibition. This vegetative background promotes BA development, mucus hypersecretion by the bronchial glands, dyscrinia as was found in the patients under examination. It also leads to a lack of the GB contractility, development of sphincter of Oddi hypertension dysfunction, and CAC. The distribution of patients according to the severity of asthma and correlation analysis showed a direct interdependence between the severity of asthma (by FEV_1 index-forced expiratory volume) of AChE activity ($r = 0.784$, $p < 0.05$).

An analysis of the studies showed significant changes in the CDE of the surveyed individuals. For instance, the CDA in the individuals of groups 1 and 2 was lower by 1.6 and 2.4 times respectively ($p < 0.001$) than in the group of PHI; in the patients of the 3rd group – the changes were minor – a decline of 14.6% ($p<0.05$) compared with practically healthy individuals (Table 1). It should be noted, that the CDE in the first group was 64. 9% lower than in the second one. The patients of the first group had a particular catecholamine (CA) depositing intensity depending on the presence of the concomitant CAC. For instance, the patients with an isolated BA had a significantly lower CA (by 1.5 times) per one erythrocyte ($p<0.05$). The patients, suffering from BA combined with CAC, had by 3 times less CA per one erythrocyte ($p<0.05$) than normal indices, and that was by1.5 times less than in the first group patients ($p<0.05$). The above mentioned changes occur in the patients of the 3d group too. The number of CA in an ordinary erythrocyte becomes a little less (for 13%) ($p<0.05$). Participation of sympatho-adrenal system in the pathogenesis of asthma

Table1

Indices of catecholamine depositing function of erythrocytes, of the acetylcholinesterase activity and of the cortisol amount in the blood in patients with bronchial asthma combined with chronic acalculous cholecystitis, depending on bronchial asthma severity rate, (M±m)

Indices	PHI, n=30	BA II degree n=16	BA III degree, n=14	BA II degrre and CAC n=12	BA III degree and CAC n=18
Number of CA in 1 er.	3,15±0,051	2,45± 0,042*	1,84± 0,038*/**	1,27± 0,016*/**/***	0,95±0,05 */**/***/#
AChE, micromole /h/l	220,75± 4,342	169,28± 5,632 *	132,43±3,512 */**	124,75±3,124 */**/***	118,75±2,135 */**/***/#
Cortisol nanomole /l	421,23± 12,451	184,15± 8,213*	153,35±9,024 */**	132,89±8,385 */**/***	105,14±6,115 */**/***/#

Annotation: * – reliability of the difference as compared to the healthy individuals group;
** – The differences are reliable compared to the indices in the patients with the II degree BA;
*** – The differences are reliable compared to the indices in the patients with the III degree BA;
# – The differences are reliable compared to the indices in the patients with the II degree BA combined with CAC

Table 2

Indices of correlation between the indications of catecholamine depositing function of erythrocytes, acetylcholinesterase activity, amount of cortisol in the blood, as well as the external respiration, erythrocyte morphofunctional properties in patients with bronchial asthma and chronic acalculous cholecystitis

Index and the patients' group	Correlation index	P value
FEV_1-CDE	0,732	< 0,01
FEV_1AChE	0,628	< 0,01
FEV_1-cortisol	0,833	< 0,01
CDE- GB contractility index	0,627	< 0,01
CDE- CE	0,613	< 0,01
CDE-LI	0,525	< 0,01
AChE-duration of the 2nd phase of choleresis	-0,836	< 0,01
AChE- LI	0,738	< 0,01
Amount of cortisol in the blood and of sialic acids in the bile	-0,725	< 0,01

occurrence has been proved, however, in patients with asthma and CAC, the ability to deposit CA, when combined with CAC has significantly dropped.

The study of cortisol density in the blood serum of the patients under examination showed its significant drop in all groups observed (table 1). For instance, the first group patients' blood contained 2.7 times ($p<0,05$) less cortisol than that of PHI; in the patients of the second group the inhibition of the functional state of the adrenal cortex was even more intense – cortisol was lower than its index in the control group by 3.7 times ($p<0,05$); the 3d group patients had the maximum drop in cortisol secretion by 1.7 times ($p<0,05$) with reliable intergroup difference (Table 1). Thus, one of the risk factors for BA development is a significant inhibition of cortisol-synthetic adrenocortical function. This is, probably, one of the pathogenic mechanisms of BA, and, in particular, the progression of bronchial inflammation and formation of в-adrenergic mediators, insensible to the influence of sympathoadrenal system, and of facilitating adrenergic imbalance. The results of the study of cortisol amount in patients, suffering from BA combined with CAC depending on the BA severity rate, prove this hypothesis.

In particular, the patients with BA of II degree had lower cortisol concentration in their blood than those of the PHI group by 2.3 times ($p<0,05$), the same index in the patients with BA of III degree was lower by 2.8 times($p<0,05$), besides, in the patients with BA of II degree there was a reliably maximum decrease of cortisol and of synthetic adrenocortical function – by 3.7 times ($p <0.05$) with the presence of reliable intergroup differences ($p <0.05$). The correlation analysis indicates a significant direct relationship between the FEV_1 index and cortisol levels in patients with BA combined with CAC ($r = -0,725$, $p <0,05$). Thus, the patients under the study experienced a significant inhibition of synthesis and decrease in blood cortisol, which correlates with the severity of asthma and is a risk factor for progression of an inflammation in the GB. Table 2 shows a matrix of correlations between indices of CDE, AChE activity, cortisol levels and indices of lung function, morphological and functional properties of erythrocytes in patients with asthma and CAC.

According to statistical data, there is a tight direct correlation between FEV_1 indices and the cortisol amount in the blood, AChE and CDE activity, that is, adrenal insufficiency(cortisol deficiency in the blood), reduced AChE activity, intensifying vagotonia, as well as an increasing resistance to CA (reduced CDE) all contribute to BA and CDE development. CDE indices are, to a considerable degree, interdependent with the contractibility of the GB, of choleresis effort (CE) and lithogenic index (LI). A reciprocal proportion between AChE activity indices and a duration of sphincter of Oddi spasm during the second phase of choleresis , as well as the direct interdependence between the AChE and LI activities which proves, that it is vagotonia which causes all above mentioned disorders. A negative correlation between the index of cortisol in the blood and sialic acid content indicates a direct pathogenetic basis of inflammatory changes in the GB and the bronchi.

Conclusion

The base of regulatory neuroendocrine and paracrine mecganisms imbalance, contributing to a development of bronchial asthma, is the cholinergic imbalance (reduction in blood acetylcholinesterase activity, hypertensive sphincter of Oddi dysfunction), adrenergic imbalance (reduction of reversibility of bronchospasm with inhaled β-agonists under conditions of comorbidity (12-13% vs. 16-23% for isolated asthma)), reduction in catecholamine-depositing erythrocytes function, hypokinetic gallbladder dysfunction, adrenal dysfunction (decreased cortisol levels) that contribute to the development and progression of chronic cholecystitis against a background of hypokinetic gallbladder dysfunction.

References. 1. Европейская сеть по глобальной аллергии и астме (GA2LEN) изучает «эпидемию» аллергии и астмы / Д. Буске, П.Д. Бурней, Т. Зубербир [и др.] // Пульмонология.- 2009.- №4.- С.119-126. 2. Заболевания органов пищеварения у больных бронхиальной астмой / Е.С. Галимова, Г.М. Нуртдинова, О.И. Кучер [и др.] // Фундаментальные исследования.- 2010.- №1.- С.36-40. 3. Илюхина Л.Н. Клинические и эндоскопические особенности поражения гастродуоденальной зоны у больных бронхиальной астмой / Л.Н. Илюхина, Н.П. Красавина, В.А. Башкатов // Сибирский мед. журн. (г. Иркутск).- 2010.- Т.99, №8.- С.72-74. 4. Клинические аспекты некоторых наиболее распространенных сочетаний бронхиальной астмы с заболеваниями органов брюшной полости (обзор литературы) / Е.С. Галимова, Г.М. Нуртдинова, О.И. Кучер [и др.] // Фундаментальные исследования.- 2010.- №4.- С.26-35. 5. Мурадосілова Л.І. Вплив нейроендокринних факторів на клініко-етологічні особливості бронхіальної астми у дітей: автореф. дис. на здобуття наук. ступеня канд. мед. наук.: спец. 14.01.10 «Педіатрія» / Леніє Ісметівна Мурадосілова; Кримський держ. мед. університет ім. С.І. Георгієвського МОЗ України.- Сімферополь, 2008.- 36 с. 6. Castro-Rodriguez J.A. The Asthma Predictive Index: early diagnosis of asthma / J.A. Castro-Rodriguez // Curr. Opin. Allergy Clin. Immunol.- 2011.- Vol.11, №3.- P.157-161. 7. Fanta C.H. Asthma / C.H. Fanta // N. Engl. J. Med.- 2009.- Vol.360, №10.- P.1002-1014. 8. Lang D.M. New asthma guidelines emphasize control, regular monitoring / D.M. Lang // Cleveland Clinic J. Med.- 2008.- Vol.75, №9.- P.641-653. 9. Wang X.Y. Cholinergic and nitrergic innervation of ICC-DMP and ICC-IM in the human small intestine / X.Y. Wang, C. Paterson, J.D. Huizinga // Neurogastroenterol. Motil.- 2003.- Vol.15, №5.- P.531-543.

ИЗМЕНЕНИЯ ХОЛИНЕРГИЧНОЙ, АДРЕНЕРГИЧЕСКОЙ РЕГУЛЯЦИИ ТОНУСА БРОНХОВ И ЖЕЛЧЕВЫВОДЯЩИХ ПУТЕЙ ПРИ СОЧЕТАННОМ ТЕЧЕНИИ БРОНХИАЛЬНОЙ АСТМЫ И ХРОНИЧЕСКОГО ХОЛЕЦИСТИТА

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Резюме. В статье представлены данные исследования состояния нейроэндокринной регуляции тонуса гладких мышц бронхиального дерева и желчного пузыря путем оценки состояния функционирования адренергической и холинергической систем у больных бронхиальной астмой и хроническим некалькулезным холециститом, которое показало существенные изменения адренореактивности и холинореактивности, а также изменения секреции кортизола.

Ключевые слова: бронхиальная астма, хронический некалькулезный холецистит, адренергическая и холинергическая регуляция, ацетилхолинэстераза.

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ЗМІНИ ХОЛІНЕРГІЧНОЇ, АДРЕНЕРГІЧНОЇ РЕГУЛЯЦІЇ ТОНУСУ БРОНХІВ ТА ЖОВЧОВИВІДНИХ ШЛЯХІВ ЗА ПОЄДНАНОГО ПЕРЕБІГУ БРОНХІАЛЬНОЇ АСТМИ ТА ХРОНІЧНОГО ХОЛЕЦИСТИТУ

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Резюме. У статті викладено дані дослідження стану нейро-ендокринної регуляції тонусу непосмугованих м'язів бронхіального дерева та жовчного міхура шляхом оцінки стану функціонування адренергічної та холінергічної систем у хворих на бронхіальну астму та хронічний некаменевий холецистит, яке показало істотні зміни адренореактивності та холінореактивності, а також зміни секреції кортизолу.

Ключові слова: бронхіальна астма, хронічний некаменевий холецистит, адренергічна та холінергічна регуляція, ацетилхолінестераза.

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