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Predictability and risk factors of severe bronchial asthma in children

Key words: *bronchial asthma, severe course, prognosis, children.*

Bronchial asthma (BA) – one of famous multifactorial chronic lung disease, which is formed on the combined influence of genetic susceptibility and environmental factors. The disease most often occurs in childhood, but can start at any period of life. There is a hereditary predisposition to asthma. This is evidenced by the increased incidence of asthma relatives of patients. Each year, the disease kills 100 thousand people. The average mortality rate for the data received from 48 countries, corresponding to 7.9 per 100,000 population. According VOZ more than 300 million people worldwide suffer from asthma. However, despite this, finally calculate the risk of the disease can not be like predicting the disease, especially in children [1, 2].

Severe asthma in childhood is a serious medical and social problem. If asthma begins in early childhood, the prognosis is usually favorable: in 80 % of patients until period of puberty disease disappeared or become less pronounced. Approximately 20 % of patients after 45 years of disease are recurrence. Cases recovery of adult patients with asthma observed less frequently. Children's asthma more difficult if it is combined with other allergic respiratory diseases or neurodermatitis. Mortality from asthma increases with age: in children, it is no more than 1 %, in adults – 2–4 % [3].

Severe asthma in children is a clinical form of the disease, which is characterized by constant day and night symptoms, frequent exacerbations, leading to reduced lung function parameters, a high level of bronchial hyperresponsiveness. Studies show that in the pathogenesis of asthma attracted many genes set which can vary in different ethnic groups. The study of genes associated with the development of asthma concerns 4 key areas: product immunoglobulin (Ig) E (atopy); the degree of severity of airway hyperresponsiveness; production of inflammatory mediators (cytokines and growth factors); determine the correlation between immune response and Th1-Th2-type.

Predictors of severe asthma have a high index of atopy-associated gene polymorphism of interleukin-4 (IL-4). Currently installed more than 20 genes that are associated with atopy, and more than 100 genes associated with asthma. The influence of genetic factors on the formation of asthma and its phenotype showed their considerable heterogeneity. Established gene polymorphism ADRβ2 (Arg16Gly and Glu27Gln), which defines an increased likelihood of severe asthma. (Wechsler M. et al., 2006). Moreover, gene IL-4 receptor (IL4RA) and gene FcεRI β (encoding β-subunit receptor IgE), can be attributed to atopy genes and gene ADRβ2 - to genes bronchial hyperresponsiveness [3, 4].

There is a high index of atopy known today as a predictor of severe asthma, as evidenced by the results of several studies, is to deploy the disease phenotype requires a genetic predisposition and exposure to adverse environmental factors. Genetic markers were studied in a number of scientific works of local and foreign researchers. Thus, in many studies there are indications of severe asthma association in children and IL-4 gene, polymorphism due 590T and 717S G + IL-4 gene, HLA-DRB1 genotype; high levels of Ig E (510 IU/ml with severe and 198 IU/ml in medium-heavy BA); high levels of IL-4 (189 pg/ml in severe and 47 pg/ml in medium-heavy BA); BA mother; concomitant atopic dermatitis. There are several groups of candidate genes for asthma – a key genes (genes cytokines – IL4, IL17A, IL17F) and heny-"modifiers" (detoxification system genes – CYP1A1). A lot of studies genes cytokine networks that play a crucial role in the development of allergic inflammation of the bronchi. However, just

as genes interact with each other, and how these factors affect the environment are still unknown. Detection of high-level Ig E in a child with asthma, which supported hereditary history on the mother is high risk factors of rapidly progressive inflammation, uncontrolled growth of severe asthma [5, 6].

In numerous association studies have shown that in the pathogenesis of asthma involved many functionally interrelated genes (gene networks), including the main key genes and gene-modifiers phenotypic effect depends on environmental factors. The most informative to identify risk factors of asthma is uncontrolled population and family studies that together with molecular genetic analysis widespread in the last decade [4, 6]. There is a method of estimating the genotypic values of the parameters respiratory function of the child on the basis of phenotypic indicators of his parents. This forecasting model has advantages over existing methods of assessing the hereditary predisposition, as it allows to quantify the risk of uncontrolled genome of asthma [6].

In order to prognosis of asthma should take into account clinical and functional parameters, especially the psychoemotional and social status. Today had been developed a two-stage algorithm for prediction of asthma based on clinical and functional characteristics of asthma in children depending on the severity and control of symptoms of the disease based on the study of predictors that determine it. Based on mathematical modeling using multivariate analysis systematized many potential factors that predict course of asthma, defined their predictive weight and developed a system of medical and social prognosis of asthma in children. Using multidimensional nonlinear regression analysis identified total prognostic criteria: medical and social (MSPC) and bodypletismografia (BPPC) compiled a two-stage algorithm for prediction of asthma with the definition of individual prognostic risk index (PRI) development of asthma and evaluation of basic treatment dynamics. Thus, the authors determined the relationship between course of clinical manifestations of asthma and degree of ventilation disorders according bodypletismografia depending on period of disease and control of asthma symptoms [1].

There are other factors which contribute to the development of severe asthma in children: sinusitis, various upper respiratory tract infection, dysfunction of vocal cords, contact with allergen, emotional and psychological factors, excessive use of beta2-agonists, smoking (passive and active), low complaence, socio-economic, ethnic factors (African-American children). Many of these factors affect both occurrence of disease and on its course. For example, smoking is a factor that leads to asthma, but also significantly affect course of disease. Up to 15 % cases of severe asthma may be associated with ongoing contact with allergen, although in daily practice rarely recognized this fact. A significant number of cases of atopic asthma remains discovered cause and significant allergen [1]. In the case of severe asthma need to recognize the importance of careful monitoring of all possible triggers, including allergens, particularly mold Alternaria Alternata, which is a major allergen sensitivity which is associated with very severe and fatal asthma [1, 11].

Gastroesophageal reflux often found in patients with asthma. As you know, this condition occurs in 60% of children with moderate and severe asthma. At this time, no known clear linkages reflux disease and worsening of asthma, but asthma marked improvement in effective treatment of this disease. Viral and bacterial infections sinuses are considered as possible factors exacerbation of asthma, but their precise role in evelopment of severe asthma are not identified.

Psychological factors such as social deprivation, often ignored by clinicians associated with poor asthma control. In patients aged 6–18 years high levels of panic and fear associated with a high risk of hospitalization. The conflict between parents and doctor about treatment of child, poor self-service hospital, conflict between patient and hospital staff neglect symptoms of depression by a physician associated with a real increase in risk of death. Problems in family, loss of a close friend or family member increases their risk of ending in death. Sometimes asthma as a way of manipulating lifestyle. The ability of higher cortical centers affect synthesis of inflammatory cytokines actively studied that might help understand relationship of psychological problems and development of severe asthma in many patients [1].

Another factor in development of severe asthma may be over-beta2-agonist. These recent studies show that use of more than two beta2-agonist per month associated with a high risk of death [13, 15]. There are publications indicate that some patients uncontrolled asthma may be due to increased metabolism of leukotrienes. These situations can develop episodes of asthma attacks that threaten life on a background of conventional controlled disease [3, 4, 6].

Other air pollutants, endotoxins, viral respiratory infections also may increase risk of uncontrolled asthma. There is some evidence that presence of chlamydial infection contributes to development of severe forms of asthma. Low complaence patient reluctance to follow doctor's recommendations are largely associated with development of severe asthma. Pediatric asthma is more common in boys. This is due to fact that boys are late in lung structural development in early childhood compared lung girls. Severe asthma in boys leads to persistent narrowing of bronchi anatomically narrow. The narrow airways are a risk factor for fatal episodes of asthma in children. Childhood Asthma (3–10 years) were associated with the risk of fatalities in severe asthma, but there is plenty of evidence of progression of inflammation in this age group and the development of traits bronchial remodeling [3, 7, 9, 14, 15].

Today we know that in pathogenesis of asthma participate protein products of genes of xenobiotic detoxification system. A recent study Sardaryan JS (2009) studied phenotypic features of asthma in allelic gene polymorphism of glutathione-S-transferase T1 (GSTT1), glutathione-S-transferase M1 (GSTM1), angiotensin converting enzyme (ACE), endothelial nitric oxide synthase (eNOS). Found that association of genotypes GSTT1- \ GSTM1 increases 5 times the risk of asthma in children compared to the population. In children with functionally active genotype GSTT1 + \ GSTM1 + in association with polymorphism I\I ACE gene on the risk of asthma decreased by 7 times, which makes this association protective genotypes. Perhaps differences polymorphic variants of cytokine genes and enzymes detoxify play a role in shaping clinical phenotype of asthma, which according to GINA can be presented 4 forms gravity.

In group of older children (10–18 years) the most important in the clinical picture is the increased frequency of severe exacerbation of asthma. At age of peak fall in infant mortality from asthma. Increasing the role of triggering factors (depending of weather, emotional stress, physical activity, smoking, pollutants), indicating growing bronchial hyperreactivity. Severe asthma has a significant impact on quality of life. In this age group, severe asthma in some children with complications occurring. An important role in choice of treatment approaches for patients older plays a reduced sensitivity to steroids. Therefore some patients can be found resistant to treatment of severe asthma that requires modification approaches to therapy. Corticosteroid resistance is only known nowadays mechanism therapeutically-resistant asthma. Other mechanisms proposed and discussed. Primary corticosteroid resistance is rare situation in asthma. Even secondary resistance, that is end result of progressive inflammation and parallel to the development of bronchial remodeling, is not characteristic of pediatric practice [9].

Prediction of asthma in pediatrics and application techniques for the prevention of severe – and very topical task grateful for pediatric patients and physicians. The course of severe asthma has clinical features in different age groups (children's asthma, early school, teen) [10]. The basis of age heterogeneity – evolution of immune inflammation and morphological changes in bronchi, from acute and chronic inflammation in infants remodeling to schoolchildren. Scientists around the world work on finding methods, development of algorithms for prediction and prevention of severe asthma in children.

To predict asthma attacks severe course in school age children spend provocative test sulphadimezin studied using daily urine determine the percentage of acetylated sulfadimezin in urine, and in its values not exceeding 75 % of sulfadimezin urine predict severe clinical course asthma attacks [16]. Alternatively prognosis of asthma in children, is determining the state of adaptive reactions using indicators ECG, characterized in that state changes in the function of autonomic nervous system, relevant to type of disease and the detection of nervous system, moderate situational anxiety level and type the first unit to respond to disease predict mild course, while high level reactivity of autonomic nervous system, high levels of situational anxiety and a second or third unit response – medium-severe course of asthma in children [17].

Inventors Wolf Y. O. proposed way of predicting severe genetically determined atopic asthma in children with dermato-respiratory syndrome, involves use of polymerase chain reaction, characterized in that calculated risk of realization of asthma in children with atopy severity scale criteria by assigning each evaluation criteria from 0 to 2 points, making table with our performance, processing and systematization of results, mild atopic responsible score from 0 to 5, moderate form – 5–10 points, severe atopy – more than 10 points, in addition, children with severe atopy, conducting polymerase chain reaction for detection of single nucleotide polymorphisms Asp299Gly gene Toll-like receptor 4 (position 1187, rs4986790), detection of allele G TLR4 certifies and is associated with severe course of atopic asthma [18].

Inventors of Vinnitsa National Medical University developed a number of methods on early detection of risk of asthma in urban children older school children of different gender prediction method in urban primary school children of both sexes by forecasting, early prediction of the risk of asthma in rural adolescents of both sexes and among rural children primary school children of both sexes which consist in defining a set of performance features finger and palmar dermatoglyphics, carried out stepwise discriminant analysis and, therefore, create mathematical models of prognosis using equations [3, 4, 6, 7]. Early determination risk of asthma in rural primary school children of both sexes, in rural adolescents of both sexes in urban children and adolescents in urban elementary school children also perform forecasting method, which is defining a set of anthropometric indicators and somatotypological, carried out stepwise discriminant analysis and create mathematical models of prognosis using equations [19–22].

Method of predicting a high probability of a child with asthma by history taking and laboratory studies wherein find that a history burdened heredity through the maternal line on chronic broncho-obstructive disease and presence of a child signs of bronchial obstruction, examine level of total immunoglobulin E in blood and in presence of maternal grandmothers asthma or chronic obstructive pulmonary disease and at least one episode of bronchial obstruction in a child and total immunoglobulin E levels above 300 IU/ml defining high risk of asthma in child [23].

In Russia developed a promising method forecasting severity of asthma in adolescents in puberty by determining level of thyroid hormones triiodothyronine (T3, U/l) and thyroxine (T4 in, U/l), pituitary hormones – TTH hormone (TSH, U/l), follicle-stimulating hormone (FSH in IU/ L) and lyuteineziruyuchoho hormone (LH in mIU/ml) radioisotope method and level of physical development of the adolescent definition somatotype where mikrosomatotypu equals 1, mezosomatotypu – 2 makrosomatotypu – 3. Decide discriminant equation for boys is as follows: $D = 19{,}535 \times (T3) + 3{,}973 \times (T4) - 27{,}38 \times (TSH) - 11{,}028 \times (1, 2 \text{ or } 3) - 307{,}473 \times (FSH) - 17{,}585 \times (LH)$, and a value of discriminant function $D > 116{,}44$ predict worsening of asthma, and when $D < 116{,}44$ predict improvement of asthma. Girl equation is: $D = -4{,}908 \times (T3) - 0{,}052 \times (T4) - 0{,}355 \times (TSH) - 3{,}166 \times (1, 2 \text{ or } 3) - 0{,}769 \times (FSH) - 0{,}144 \times (LH)$, meaning $D > -24{,}23$ predict worsening of asthma, and when $D < -24{,}23$ predict improvement of asthma. The method allows to detect differentially teenagers, threat on the development and course of severe asthma [24].

Numerous scientific studies have shown that in the pathogenesis of asthma attended a lot of functionally related genes (gene associations), including existing main, key genes and genes – modifiers phenotypic effect depends on environmental factors. Currently installed over 20 genes associated with atopy and 100 candidate genes associated with bronchial asthma. The influence of genetic factors on the asthma phenotype are different. The most informative to identify risk factors for severe bronchial asthma are population and family studies. These studies and molecular genetic analysis are widely used in the last decade.

Studies show that in the pathogenesis of bronchial asthma involved multiple genes. Geves are different in different ethnic groups. Research of genes associated with the development of asthma, concerns four key issues: product immunoglobulinum E (Ig E) (atopy); the level severity of airway hyperresponsiveness; production of inflammatory mediators (cytokines and growth factors); determining the ratio between immune responses Th1 and Th2-type. Modern research shows that the propensity to develop severe bronchial asthma in children are caused by the genotype of atopy (level of IL-4, IgE, atopic diseases in the family). Established gene polymorphism ADRβ2 (Arg16Gly and Glu27Gln) determined an increased chance of developing severe asthma. The gene IL-4 receptor (IL4RA) gene FcεRI β (β-subunit encodes a high affinity receptor for IgE), can be attributed to atopy genes and gene ADRβ2 – to genes bronchial hyperreactivity.

We know today that in the pathogenesis of asthma involves the protein products of genes xenobiotic's detoxification. Recent studies have examined the phenotypic characteristics of bronchial asthma with allelic polymorphisms of genes glutathione - S- transferase T1 (GSTT1), glutathione – S-transferase M1 (GSTM1), angiotensin converting enzyme (ACE), endothelial nitric oxide synthase (eNOS). Revealed that the association of genotypes GSTT1- \ GSTM1 increases in 5 times the risk of asthma in children compared with the population. If children have functional activity genotype GSTT1 + \ GSTM1 + in association with polymorphism I \ I gene ACE risk of asthma decreased by 7 times. So, this association is protective genotypes for risk of asthma in children. Perhaps differences polymorphisms of cytokine genes and enzymes detoxify play a role in shaping the clinical phenotype of asthma, which, according to international consensus on asthma (GINA) can be represented by four forms of gravity.

In order to predict the course of disease in general, and severe bronchial asthma, in particular, must take into account the clinical and functional parameters, especially psychoemotional and social status of the patients, influence of environmental factors and heredity. Today is actively studied ability of higher cortical centers of influence on synthesis of pro-inflammatory cytokines that may allow us to understand relationship of psychological problems and poor control of asthma in a lot of patients.

Thus, it is clear that the development of bronchial asthma and a variety of its clinical polymorphism genes affected by the presence of numerous different chromosomes. Therefore, probability of establishing asthma as polygenic inheritance of the disease by testing a single gene is severely limited, both for diagnosis and for its prevention. Prediction of bronchial asthma is better to build on an assessment of complex genes, characteristics of human body and environmental risk factors.

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ВОЗМОЖНОСТИ ПРОГНОЗИРОВАНИЯ И ФАКТОРЫ РИСКА ТЯЖЕЛОГО ТЕЧЕНИЯ БРОНХИАЛЬНОЙ АСТМЫ У ДЕТЕЙ

Л. Б. Ярощук

Резюме

В статье представлен обзор результатов научных исследований по вопросам возможности прогнозирования и поиска факторов риска развития бронхиальной астмы (БА) в целом и ее тяжелого течения у детей в частности. В многочисленных научных исследованиях показано, что в патогенезе БА принимают участие множество функционально взаимосвязанных генов (генных ассоциаций), в том числе существуют главные, ключевые гены и гены-модификаторы, фенотипический эффект которых зависит от факторов окружающей среды. В настоящее время установлено более 20 генов, ассоциированных с атопией, и более 100 кандидатных генов, связанных с БА. Исследование влияния генетических факторов на формирование БА и ее фенотип показало их значительную гетерогенность. Наиболее информативными для выявления факторов риска развития тяжелого течения БА является популяционные и семейные исследования, которые наряду с молекулярно-генетическим анализом получили широкое распространение в последнее десятилетие.

Результаты исследований показывают, что в патогенез БА вовлечено множество генов, набор которых может различаться в разных этнических группах. Изучение генов, связанных с развитием БА, касается 4 ключевых вопросов: продукции аллергенспецифичных иммуноглобулинов (Ig)E (атопия); степени выраженности гиперреактивности дыхательных путей; продукции медиаторов воспаления (цитокинов и факторов роста); определение соотношения между иммунными реакциями Th1- и Th2-типа. Современные исследования показывают, что склонность к развитию тяжелого течения БА у детей обусловлена генотипом атопии (уровень IL-4, IgE, атопические заболевания в семье). Установлено, что полиморфизм гена ADRβ2 (Arg16Gly и Glu27Gln) определяет повышенную вероятность развития тяжелой БА. Причем ген рецептора IL-4 (IL4RA) и ген FcεRIβ (кодирует β-субъединицу высокоаффинного рецептора к IgE) могут быть отнесены к генам атопии, а ген ADRβ2 – к генам бронхиальной гиперреактивности.

На сегодняшний день известно, что в патогенезе БА участвуют белковые продукты генов системы детоксикации ксенобиотиков. Недавними исследованиями изучены фенотипические особенности БА при аллельных полиморфизмах генов глутатион-S-трансферазы T1 (GSTT1), глутатион-S-трансферазы M1 (GSTM1), ангиотензинпревращающего фермента (ACE), эндотелиальной синтазы оксида азота (eNOS). Выявлено, что ассоциация генотипов GSTT1^{-}\GSTM1 повышает в 5 раз риск развития БА у детей по сравнению с общей популяцией. У детей при функционально активном генотипе GSTT1^{+}\GSTM1^{+} в ассоциации с полиморфизмом I\I по гену ACE риск развития астмы снижается в 7 раз, что позволяет считать эту ассоциацию генотипов протективной. Возможно, различия полиморфных вариантов генов цитокинов и ферментов детоксикации играют определенную роль в формировании клинического фенотипа БА, который согласно Международному консенсусу по бронхиальной астме (GINA) может быть представлен 4 формами тяжести.

С целью прогнозирования течения заболевания вообще и тяжелого течения БА в частности необходимо учитывать клинико-функциональные параметры, особенности психоэмоционального и социального статуса пациентов, влияние окружающей среды, а также факторы наследственности. Сегодня активно изучается способность высших корковых центров влиять на синтез противовоспалительных цитокинов, что, возможно, позволит понять взаимосвязь психологических проблем и плохого контроля астмы у многих пациентов.

Итак, понятно, что на развитие БА и разнообразие ее клинического полиморфизма влияет наличие многочисленных генов различных хромосом. Поэтому вероятность установления астмы как болезни полигенного наследования путем тестирования единственного гена сильно ограничена как для диагностики, так и для ее профилактики. Прогнозирование течения БА целесообразно строить на оценке комплекса генов, особенностей организма человека и факторов риска окружающей среды.

Ключевые слова: *бронхиальная астма, тяжелое течение, прогнозирование, дети.*

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PREDICTABILITY AND RISK FACTORS OF SEVERE BRONCHIAL ASTHMA IN CHILDREN

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Summary

The article provides an overview the results of research on the possibility and risk factors for asthma in general, and of severe bronchial asthma in children in particular. Numerous scientific studies have shown that in the pathogenesis of asthma attended a lot of functionally related genes (gene associations), including existing main, key genes and genes-modifiers phenotypic effect depends on environmental factors. Currently installed over 20 genes associated with atopy and 100 candidate genes associated with bronchial asthma. The influence of genetic factors on the asthma phenotype are different. The most informative to identify risk factors for severe bronchial asthma are population and family studies. These studies and molecular genetic analysis are widely used in the last decade.

Studies show that in the pathogenesis of bronchial asthma involved multiple genes. Geves are different in different ethnic groups. Research of genes associated with the development of asthma, concerns four key issues: product immunoglobulinum E (IgE) (atopy); the level severity of airway hyperresponsiveness; production of inflammatory mediators (cytokines and growth factors); determining the ratio between immune responses Th1- and Th2-type. Modern research shows that the propensity to develop severe bronchial asthma in children are caused by the genotype of atopy (level of IL-4, Ig E, atopic diseases in the family). Established gene polymorphism ADRβ2 (Arg16Gly and Glu27Gln) determined an increased chance of developing severe asthma. The gene IL-4 receptor (IL4RA) gene FcεRI β (β-subunit encodes a high affinity receptor for IgE), can be attributed to atopy genes and gene ADRβ2 – to genes bronchial hyperreactivity.

We know today that in the pathogenesis of asthma involves the protein products of genes xenobiotic's detoxification. Recent studies have examined the phenotypic characteristics of bronchial asthma with allelic polymorphisms of genes glutathione-S-transferase T1 (GSTT1), glutathione-S-transferase M1 (GSTM1), angiotensin converting enzyme (ACE), endothelial nitric oxide synthase (eNOS). Revealed that the association of genotypes $GSTT1^{-}$\GSTM1 increases in 5 times the risk of asthma in children compared with the population. If children have functional activity genotype $GSTT1^{+}$\$GSTM1^{+}$ in association with polymorphism I\I gene ACE risk of asthma decreased by 7 times. So, this association is protective genotypes for risk of asthma in children. Perhaps differences polymorphisms of cytokine genes and enzymes detoxify play a role in shaping the clinical phenotype of asthma, which, according to international consensus on asthma (GINA) can be represented by four forms of gravity.

In order to predict the course of disease in general, and severe bronchial asthma, in particular, must take into account the clinical and functional parameters, especially psycho- emotional and social status of the patients, influence of environmental factors and heredity. Today is actively studied ability of higher cortical centers of influence on synthesis of pro-inflammatory cytokines that may allow us to understand relationship of psychological problems and poor control of asthma in a lot of patients.

Thus, it is clear that the development of bronchial asthma and a variety of its clinical polymorphism genes affected by the presence of numerous different chromosomes. Therefore, probability of establishing asthma as polygenic inheritance of the disease by testing a single gene is severely limited, both for diagnosis and for its prevention. Prediction of bronchial asthma is better to build on an assessment of complex genes, characteristics of human body and environmental risk factors.

Key words: *bronchial asthma, severe course, prognosis, children.*

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