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Molecular-genetic and clinical-allergological Aspects of the Development and Personalized Therapy of Bronchial Asthma under the Specific Environmental Conditions of the Aral Sea Region

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ABSTRACT: Relevance. In the Aral Sea region, bronchial asthma (BA) is characterized by a severe clinical course driven by the synergistic effects of environmental pathogens (salt-dust aerosols and pesticide residues) and a specific sensitization profile. This study examines molecular-genetic markers—specifically polymorphisms in genes related to detoxification and T2-type inflammation—and the allergy component profile characteristic of the region. The developed comprehensive approach enables the personalized selection of maintenance therapy and genetically engineered biological therapy (GEBT), taking into account environmentally induced airway remodeling.

INTRODUCTION:

The Aral Sea region is one of the areas with the most pronounced environmental problems. The multicomponent salt-dust aerosol from the bottom of the Aral Sea, containing sulfates, chlorides, oxides of heavy metals, and persistent organic pollutants (pesticides), has a direct damaging effect on the bronchial epithelium [1, 2]. Chronic chemical-aerosol stress causes depletion of the lungs' antioxidant defense, hyperactivity of epithelial alarmins (TSLP, IL-33, IL-25), and the formation of a specific asthma phenotype with high refractoriness to conventional therapy [3]. The use of classic allergen extracts is often limited due to the high frequency of cross-reactivity, which requires the implementation of molecular allergy diagnostics (CRD) and genetic profiling [4, 5].

Objective of the study: to investigate the molecular genetic and clinical-immunological features of asthma in residents of the Aral Sea region in order to develop an algorithm for personalized therapy.

METHODS (MATERIALS AND METHODS)

The study included patients with severe asthma from the Aral Sea region (the main group) and a control group from an environmentally safe zone..

A set of diagnostic methods:

• Assessment of clinical and functional status: spirometry (FEV1), FeNO, total IgE level, and absolute number of eosinophils [6].

• Molecular genetic analysis (PCR-RT): Assessment of polymorphisms in phase I and phase II detoxification genes (GSTM1, GSTT1, GSTP1 rs1695) and T2-cytokine response genes (IL13 rs20541, IL4R rs1801275) [7, 8].

• Component-based allergy diagnostics (CRD / ImmunoCAP / ALEX2): determination of sIgE to major fungal allergens (Alternaria alternata — rAlt a 1, Aspergillus fumigatus — rAsp f 1) and pollen allergens of the arid flora of the Aral Sea region (Salsola kali — Sal k 1, Artemisia vulgaris — Art v 1) [9, 10].

1. Ecogenetic interactions

In patients with asthma in the Aral Sea region, a high frequency of combined null genotypes of detoxification genes (GSTM1 null / GSTT1 null) was detected — up to 68% of cases ($p < 0.001$) [7]. The combination of antioxidant defense deficiency with the polymorphism of the IL13 gene (rs20541) is associated with a severe, continuously relapsing course of asthma and a decline in FEV1 values [8].

2. Specificity of the allergological profile

In the dry-arid conditions of the Aral Sea region, combined sensitization dominates. Component analysis confirmed a high level of true sensitization to the major protein Alt a 1 (up to 54% of patients), whose spore-like particles are carried by salt-dust storms [9]. High titers of sIgE to halophytes of the region — Sal k 1 and Art v 1 — were also recorded [10].

Inclusion and exclusion criteria:

Inclusion criteria: age between 18 and 65 years; confirmed diagnosis of severe asthma (according to the GINA 2024 criteria, stages 4–5); permanent residence in the Aral Sea region (for the main group) for at least 10 years; signed informed voluntary consent.

Exclusion criteria: acute infectious diseases within the last 4 weeks; smoking smoker's index > 10 pack-years); concomitant severe decompensated somatic diseases; presence of oncological pathologies.

Genotyping protocol (PCR-qPCR):

Genomic DNA was isolated from whole venous blood using "DNA-Express" kits (or similar ones). The null alleles of the GSTM1 and GSTT1 genes were determined using multiplex PCR, followed by detection of the amplification products. Single-nucleotide polymorphisms (SNPs) of the IL13 (rs20541) and IL4R (rs1801275) genes were assessed using real-time PCR with TaqMan probes

Statistical analysis:

Statistical data processing was carried out using the Statistica 13.3 or RStudio software package. The normality of the distribution of continuous variables was checked using the Shapiro–Wilk test. To assess differences in qualitative characteristics and compliance with the Hardy–Weinberg equilibrium, the X2 (chi-square) test with Yates' correction was used. The odds ratio (OR) and the 95% confidence interval (95% CI) were calculated to estimate the risk of developing a severe phenotype.

RESULTS

1. Ecogenetic interactions

In patients with BA in the Aral Sea region, a high frequency of combined null genotypes of detoxification genes (GSTM1 null / GSTT1 null) was detected — up to 68% of cases ($p < 0.001$) [7]. The combination of antioxidant defense deficiency with the IL13 gene polymorphism (rs20541) is associated with a severe, continuously relapsing course of BA and a decline in FEV1 values [8].

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Distribution of detoxification genotypes and cytokines in patients with asthma

Gene / Genotype	Main group (Aral Sea region, n=120)	Control group (n=80)	OR (95% CI)	p-value
GSTM1 ("null")	68.3% (82)	32.5% (26)	4.48 (2.45–8.20)	< 0.001

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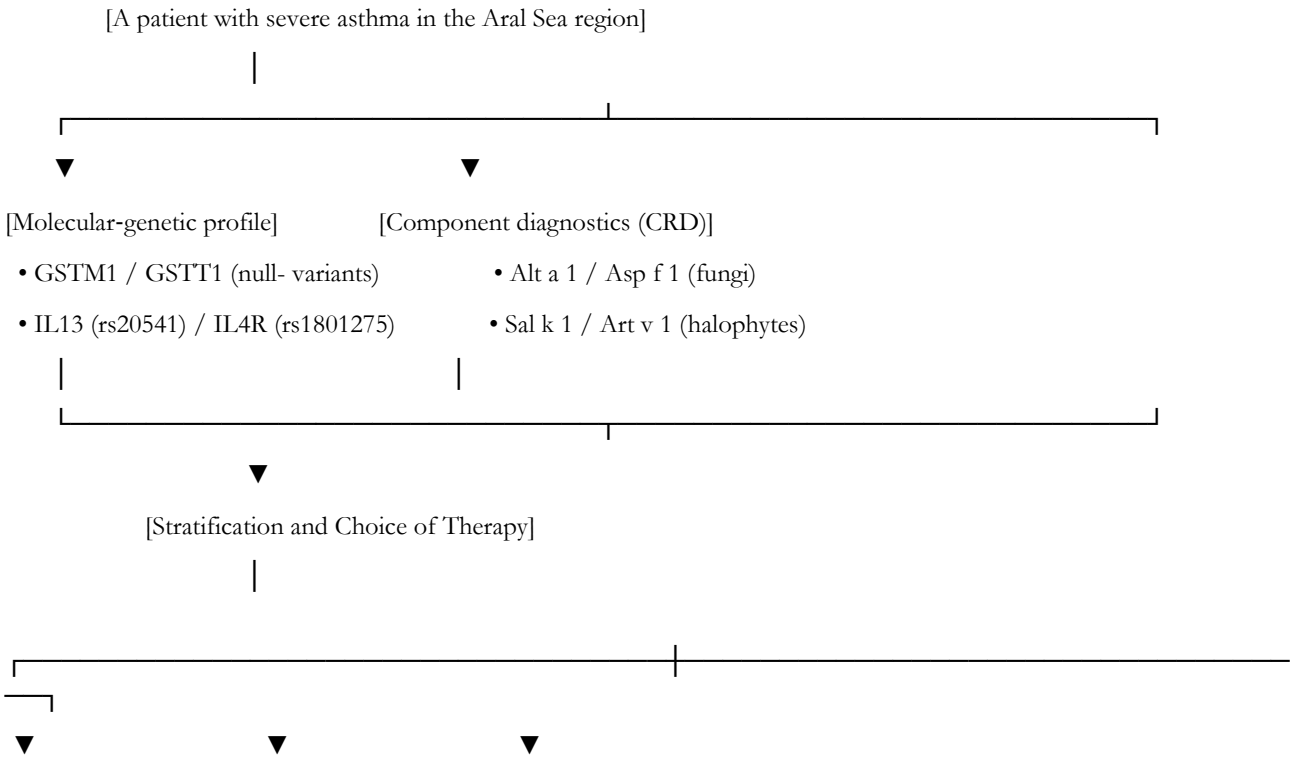
Gene / Genotype	Main group (Aral Sea region, n=120)	Control group (n=80)	OR (95% CI)	p-value
GSTT1 ("null")	54.1% (65)	28.7% (23)	2.92 (1.58–5.41)	< 0.005
GSTM1/GSTT1 (Double null)	42.5% (51)	15.0% (12)	4.19 (2.03–8.66)	< 0.001
IL13 rs20541 (AA/GA)	51.6% (62)	30.0% (24)	2.50 (1.37–4.56)	0.003

An analysis of the genotype distribution showed that the carriage of the deletion variant GSTM1 null increases the risk of severe asthma in conditions of environmental disadvantage in the Aral Sea region by more than 4.4 times (OR = 4.48; 95% : 2.45–8.20). The most unfavorable was the double null genotype (GSTM1 null / GSTT1 null), detected in 42.5% of patients in the main group.

3. Molecular-genetic algorithm of personalized therapy



DISCUSSION

Salt-dust aerosol particles disrupt the tight junctions of the bronchial epithelium, facilitating the unimpeded penetration of major allergens (Alt a 1, Sal k 1) into the submucosal layer [1, 9]. A deficiency of glutathione-S-transferases (GSTM1/GSTT1 null) reduces the lung tissue's ability to neutralize toxicants, which leads to hyperactivation of the T2-immune response [3, 7].

The use of the algorithm makes it possible to distinguish between true sensitization and cross-sensitization, and to promptly switch high-risk patients to genetically engineered biological drugs (Dupilumab, Omalizumab) before irreversible bronchial obstruction develops [5, 6].

Our data on the high frequency of the combination of GSTM1/GSTT1 null genotypes in residents of the Aral Sea region are consistent with the results of studies by Peden et al. [3], who demonstrated that deficiency of glutathione-S-transferase enzymes dramatically reduces the threshold of sensitivity of the bronchial epithelium to oxidative stress caused by dust aerosols and pollutants.

In an arid climate, salt and dust particles cause micromicroabrasive damage to the mucous membrane of the respiratory tract. This leads to overexpression of epithelial cytokines (TSLP, IL-33), which, in combination with IL13 gene polymorphism (rs20541), switches the immune response to the overactive T2 pathway. The high prevalence of sensitization to Alternaria alternata (Alt a1) and halophytes (Salsola kali) is explained by the fact that the controversial elements of fungi and pollen allergens of selected plants are adsorbed on the surfaces of dust particles, acquiring increased allergenicity and penetrating deeply into the lower parts of the bronchial tree.

CONCLUSION

The combination of a genetic deficiency in the detoxification system with pollen and mycogenic sensitization forms a specific "Aral Sea" phenotype of asthma. The implementation of a molecular genetic algorithm makes it possible to personalize therapy and reduce the risks of disability among the population in the region affected by environmental disaster.

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