

O.I. Muradova¹, L.S. Namazova-Baranova^{1,2,3}, G.A. Karkashadze¹, O.I. Maslova¹, R.M. Torshkhoeva¹, A.Y. Tomilova^{1,2}, A.A. Alexeeva^{1,2}, T.V. Turti¹, E.A. Vishneva¹

¹ Scientific Center of Children's Health, Moscow, Russian Federation

² Sechenov First Moscow State Medical University, Russian Federation

³ Pirogov Russian National Medical Research University, Moscow

Effect of allergen-specific immunotherapy courses on cognitive activity in children with pollinosis

Author affiliation:

Muradova Ol'ga Islamovna, MD, research scientist at the cognitive pediatrics department of the research institute of preventive pediatrics and medical rehabilitation of the SCCH (Federal State Budgetary Institution)

Address: 2 Lomonosovskii Av., Moscow, 119991, **tel.:** +7 (495) 967-14-20,

e-mail: kusia0@yandex.ru, Muradova@nczd.ru

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Relevance. Allergic pathology, particularly, pollinosis, may reduce cognitive functions in children. **Objective:** study effect of allergen-specific immunotherapy on cognitive functions in children with pollinosis and relation of cognitive functions dynamics to repeated ASIT courses. **Patients and methods.** We determined condition of cognitive functions in 97 children of 8-17 years of age with pollinosis in comparison with their healthy peers using a psychophysiological computer complex "Psychomath". **Results.** We revealed reduction in cognitive activity parameters in most children with pollinosis during remission. Concurrent persisting allergic rhinitis aggravated reducing in cognitive functions parameters. **Conclusion.** We confirmed positive effect of allergen-specific immunotherapy: cognitive functions improve significantly in children with pollinosis; the effect becomes more pronounced after repeated courses.

Keywords: pollinosis, allergic rhinitis, cognitive functions, allergen-specific immunotherapy, psychophysiological computer complex "Psychomath", cognitive activity.

A steady increase in the spread of allergic diseases in children has been observed in recent years all over the world. More than 25% of children suffer from various forms of allergic pathologies [1-3].

One of the most widespread allergy manifestations is allergic rhinitis caused by pollen sensitization (pollinosis). Allergic inflammation occurring in response to pollen allergens is the basis of its clinical manifestations. The disease is widespread in most countries; it affects 10-25% of the population in Russia [2]. Pollinosis manifestations are caused by inflammatory mucosal alterations, especially in the respiratory tract and conjunctivae. The most widespread symptoms of this disease are allergic rhinitis (95-98%) and conjunctivitis (91-95%) [3].

Identification and study of cognitive disorders occurring at various allergic diseases in children is one of the promising trends of the modern science [4-6]. Despite that, there are only few studies describing children's cognitive activity at such pathologies. An earlier study revealed that cognitive functions of school-age children are not disturbed during remission of bronchial asthma and dermal respiratory syndrome (moderate and severe) [7]. However, deficiency of cognitive activity was observed at other allergic diseases. E.g., a study conducted at our Center demonstrated that 95.3% of adolescents with long-term persistent allergic rhinitis with moderate and severe perennial manifestations have cognitive malfunctions; adequate therapy with intranasal steroids results in significant improvement of cognitive functions [6, 8].

We can freely assume that pollinosis also affects cerebral cognitive activity, as persistent allergic rhinitis and pollinosis rhinitis have similar pathogenetic components [3, 9]. Cognitive activity

disorder caused by allergic rhinitis may affect school performance and lead to social deadaptation [10].

The three main pollinosis therapies are well-known: exacerbation therapy, anti-relapse treatment using pharmacological drugs and allergen-specific immune therapy (ASIT). ASIT is the only method of pathogenetic treatment of allergic diseases affecting all the pathogenetic components of an allergic inflammation and changing the nature of bodily response to a certain allergen [3, 8, 11, 12]. ASIT causes the change of T cell balance in favor of activation of type 1 T helpers and inhibition of type 2 T helpers, suppression of interleukin (IL) 4 production, increase in IL12 and interferon γ production, increase in anti-inflammatory cytokine IL10 concentration and, ultimately, reduction in immunoglobulin (Ig) E synthesis.

ASIT is prescribed to children undergoing remission of IgE-mediated allergic diseases if a causative allergen and high sensibilization due to gradual increase in the dose of the injected quality allergen drug are revealed [3, 13].

Allergen-specific immune therapy induces clinical and immunological tolerance and long-term efficacy, may prevent progression of allergic diseases and affect quality of the patient's life. Preventive effect is an important advantage of ASIT: timely begun and consistent treatment prevents development of bronchial asthma in patients with allergic rhinitis.

Favorable effect of ASIT on the course of allergic diseases in children is caused by immune system alterations. ASIT also causes certain changes in the production of total and specific IgE. It ought to be mentioned that long-term (for several years) treatment results in narrowing of the spectrum and reduction in the threshold of sensitivity to the allergens, which had previously induced high sensibilization [14].

This issue is important not only because of wide spread of pollinosis, but also due to progressive incidence rate. Development of new drugs and use of the modern highly purified allergens for ASIT expand opportunities of efficient treatment and prevention of allergic diseases, including pollinosis.

Thus, allergen-specific immune therapy is the only type of antiallergenic treatment producing a long-term preventive effect after completion of the course. Neither pharmacological drug produces such a comprehensive and long-term effect. Taking into consideration cognitive activity disorders in children with pollinosis, the writing time took up the following matter: is ASIT capable of affecting the altered cognitive functions in any way possible [15]?

This study is aimed at analyzing effect of allergen-specific immune therapy on cognitive functions in children with pollinosis and dependence of dynamics of cognitive functions on the repeated ASIT courses.

In order to do that we determined quantitative parameters of cognitive activity in children with various concurrent allergic pathologies on various ASIT stages during pollinosis remission.

PATIENTS AND METHODS

The study involved 338 8-17-year-old children: 241 psychosomatically healthy children (group I, control) and 97 children with pollinosis divided into 2 groups – the children who have (group III) and have not (group II) previously undergone ASIT. Both groups of children with pollinosis were examined twice: before and after the course of allergen-specific immune therapy (pic. 1).

Study design

Criteria of inclusion into this study:

- group I – 8-17 years of age, satisfactory and above the satisfactory acquisition of high school curriculum on the basis of pedagogical characteristics, absence of chronic somatic diseases;
- group II – 8-17 years of age, pollinosis *remission*, no ASIT courses before the inclusion to the study;

- group III – 8-17 years of age, pollinosis *remission*, ASIT courses before the inclusion to the study.

Exclusion criteria for all groups were the same – no motivation for task execution during the study of cognitive activity.

The average age of the participants was 11 years: 38 (39.2%) girls and 59 (60.8%) boys. In groups II and III pollinosis manifested itself in the form of allergic rhinitis and, rarely, conjunctivitis (36%). Group III consisted of children who had previously undergone ASIT (one or two courses).

Psychophysiological computer complex “Psychomath” (KPFK-99 Psychomath, LLC Medproject-Vita, Moscow; pic. 2) was used in our study for quantitative assessment of cognitive activity.

Examination with KPFK-99 Psychomath includes the following stages:

- 1) computer-assisted setting of tasks with visual audio signaling of varying modality (a display screen [pic. 2a] and a special control panel [pic. 2b]);
- 2) patient’s responding to signals by pressing touch sensitive buttons of the control panel with a stylus (pic. 2c);
- 3) registration of patient’s responses by the software application;
- 4) computer-assisted calculation and processing of results. These procedures ensure standardization and objectivity of the examination (maximum limitation of human factor (represented by the researcher) influence on the examination results) [16,17].

The complex offers many techniques for analyzing various cognitive functions. For purposes of this study of cognitive activity, we chose a set of the most suitable techniques (6 tasks).

1. Simple sensorimotor reaction: an extremely fast motor response to a simple light signal.
2. Static coordination test: the patient is to keep a metal tip in the illuminated test opening without touching its walls and bottom.
3. Dynamic coordination test: the patient is to carry a metal tip through a narrow polygonally curved passage without touching its walls and bottom.
4. Landolt’s rings correction test is intended for testing attention and visual space perception.
5. Mnemotest is intended for assessing visual image memory and visuospatial memory.
6. Binatest in the controlled selection mode: the patient tries to guess the key sequence (left and right control panel buttons) programmed by the application; it is intended for assessing elementary analysis abilities.

Statistical analysis

We used software application Biostatistics to perform statistical data manipulation.

Significance of differences in the results between subgroups II-before and II-after, III-before and III-after was calculated using paired Student’s t-test; we used Mann-Whitney test to analyze different variants of concurrent allergic pathologies.

RESULTS AND DISCUSSION

In the first stage of examination, we obtained cognitive activity (CA) parameters of mentally and physically healthy schoolchildren (group I; tbs. 1, 2).

Gender analysis did not reveal significant CA differences between boys and girls. CA parameters of boys and girls were subsequently merged and used as control standards.

In the second stage of examination, we examined (general allergological examination and test of cognitive activity) a group of children with pollinosis (groups II and III before the treatment course); the obtained parameters were compared with control standards. Cognitive activity was assessed using the parameters lower than the control group standards by 3 sigmas and at least 2 of the 6 aforementioned tasks (confidence interval).

We revealed reduction in cognitive activity almost 2/3 of the children with pollinosis remission, who had not previously undergone ASIT (pic. 3). Reduction in CA parameters was 3 times as rare as in the group II of children with pollinosis, who had previously undergone ASIT (18,6% in comparison with 61,1%, $p < 0,05$).

The third stage consisted in examining cognitive activity in children with pollinosis after one ASIT course and comparing the obtained parameters with the parameters before the treatment (pic. 4).

The study demonstrated that the number of children with cognitive activity disorders significantly reduced after one ASIT course. It was revealed that an ASIT course improves cognitive activity parameters in both the group of the patients who had not previously undergone ASIT (group II) and in the group of the patients who had previously undergone ASIT (group III). We used one more method to analyze ASIT influence on cognitive activity of the children with pollinosis: calculation of percent correlation of the average total (according to 6 tests) CA value of the patients with pollinosis with the average total (according to 6 tests) CA value of the control group children (pic. 5).

Statistical manipulation demonstrated that an ASIT course significantly improves cognitive activity parameters by 10% on the average (from 73.1 to 83.3%) in the children who had not previously undergone ASIT (group II) and by 12.4% in the children who had previously undergone ASIT (group III). As has been mentioned above, CA parameters in the children who had previously undergone ASIT and underwent a new treatment course (subgroup III-after), i.e. underwent more ASIT courses, were maximally close to the norm, although lower still (the difference between this subgroup and the control group was significant).

In this study we also analyzed the correlation of cognitive activity with pollinosis-concurrent allergic diseases (pic. 6) – bronchial asthma and persistent allergic rhinitis.

Cognitive activity reduction is observed in half (51%) of the children with pollinosis remission without any concurrent allergic pathology. Concurrent persistent bronchial asthma during remission does not increase the number of children with reduced CA. This fact may serve as another proof of influence of bronchial asthma on a child's CA.

CA significantly decreases and the number of children with CA deficiency increases by 26% in the event of sensibilization causing overlay of perennial manifestations of allergic rhinitis in children with pollinosis; this fact confirms the data on negative influence of persisting allergic rhinitis on children's cognitive functions.

CONCLUSION

The study revealed cognitive activity disorders at pollinosis remission. Concurrent allergic pathology (bronchial asthma) during remission does not produce a marked effect on the cognitive malfunction, whereas overlay of perennial manifestations of persistent allergic rhinitis results in significant worsening of children's cognitive activity. An important result for clinicians is that the specific pathogenetic therapy – ASIT – improves cognitive activity parameters in small patients; the more ASIT courses a child has undergone, the higher his/her cognitive activity parameters. Thus, we have expanded our idea about clinical effects of ASIT: we may speak of an additional, cognition-recovering effect. These data emphasize importance and significance of ASIT and serve as an additional reason for the use of this method of treatment in children with pollinosis.

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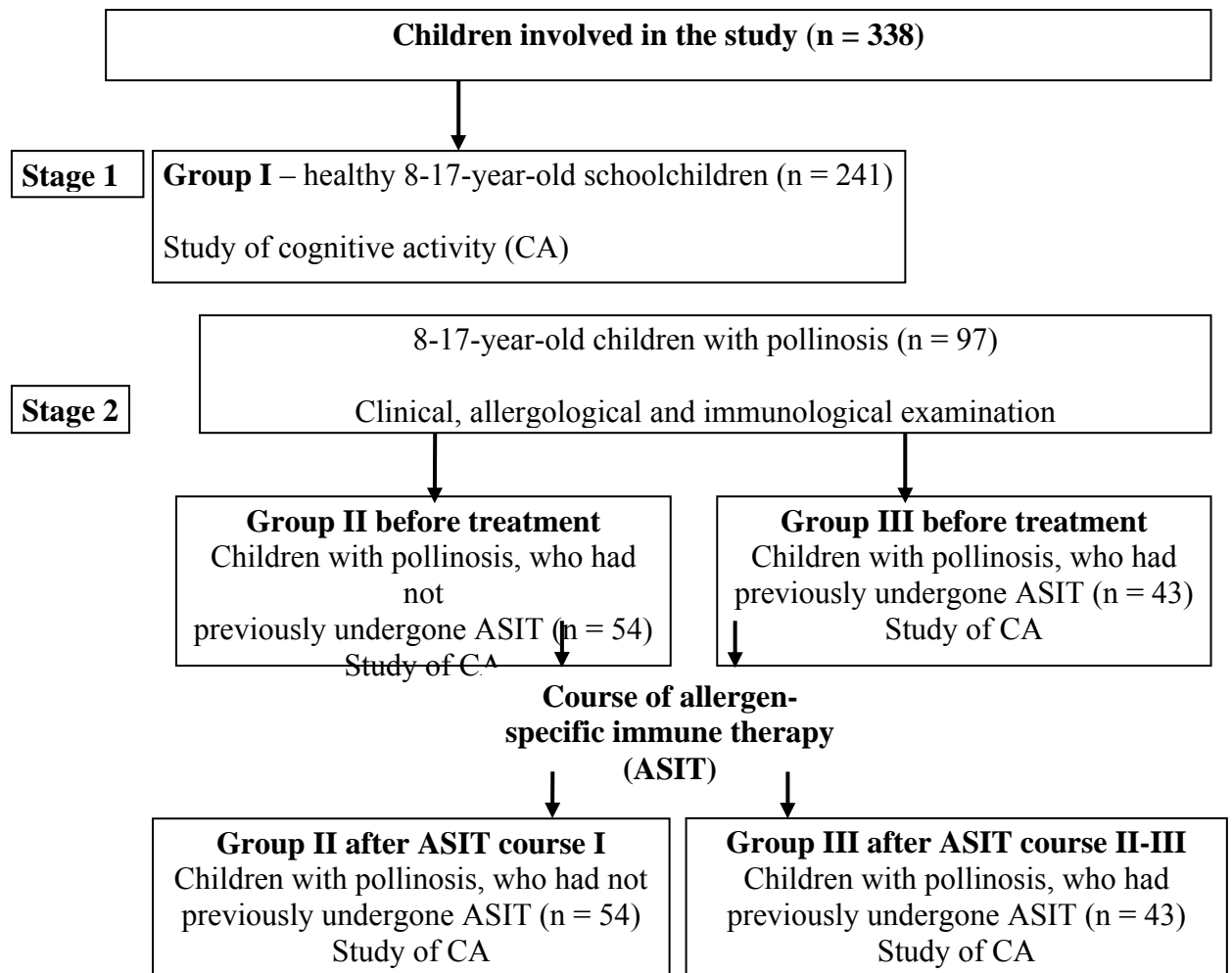
Table 1. Cognitive activity parameters in group I 8-11-year-old children

Technique	Technique parameters	8 years of age (n = 22)	9 years of age (n = 22)	10 years of age (n = 22)	11 years of age (n = 26)
Simple sensorimotor reaction	Average motor time (milliseconds [ms])	298.7 ± 32.57	238.7 ± 38.3	224.2 ± 50.8	212 ± 25
	Average latent time (ms)	287.65 ± 17.5	288.06 ± 22.3	287.8 ± 52.92	279 ± 211
Static coordination	Touch frequency (Hz)	0.68 ± 0.17	0.64 ± 0.35	0.62 ± 0.95	0.50 ± 0.20
Dynamic coordination	Integral value (%)	30.174 ± 6.14	30.14 ± 4.67	29.58 ± 13.16	30.18 ± 7.49
Landolt's rings correction test	Amount of mistakes	0.3 ± 0.25	0.33 ± 0.25	0.2 ± 0.55	0.17 ± 0.24
Binatest	Total error level (%)	-	-	-	13±8
Mnemotest	Average number of correct answers per one light image (%)	90.5 ± 8	88.5 ± 8.5	89 ± 5	94.6 ± 2.0

Table 2. Cognitive activity parameters in group I 12-17-year-old children

Technique	Technique parameters	12 years of age (n = 27)	13 years of age (n = 24)	14 years of age (n = 25)	15 years of age (n = 25)	16 years of age (n = 23)	17 years of age (n = 25)
Simple sensorimotor reaction	Average motor time (ms)	186 ± 21	188 ± 30	172 ± 23	150 ± 29	151 ± 33	140 ± 20
	Average latent time (ms)	259 ± 19	260 ± 24	262 ± 19	250 ± 22	250 ± 27	240 ± 14
Static coordination	Touch frequency (Hz)	0.54 ± 0.23	0.6 ± 0.3	0.6 ± 0.3	0.4 ± 0.3	0.2 ± 0.15	0.2 ± 0.15
Dynamic coordination	Integral value (%)	27.27 ± 5.8	27.15 ± 6.64	26.50 ± 4.9	24.73 ± 5.2	24.63 ± 8.76	23.95 ± 3.1
Landolt's rings correction test	Amount of mistakes (%)	0.18 ± 0.17	0.2 ± 0.2	0	0	0	0
Mnemotest	Average number of correct answers per one light image (%)	97.4 ± 2	99 ± 2	98.6 ± 2	100 ± 2	100 ± 2	100 ± 2
Binatest	Total error level (%)	11.6 ± 7	11 ± 6	10 ± 6	10 ± 5	8 ± 5	7 ± 4

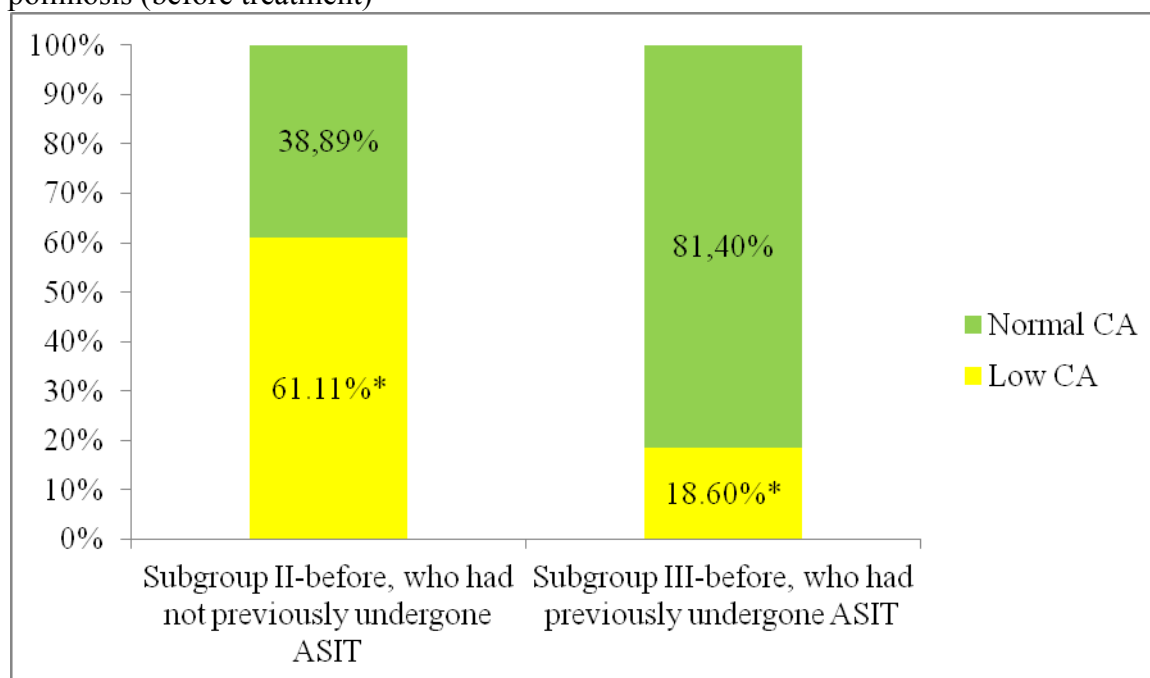
Pic. 1. Study design



Pic. 2. Complex KPFK-99 Psychomath

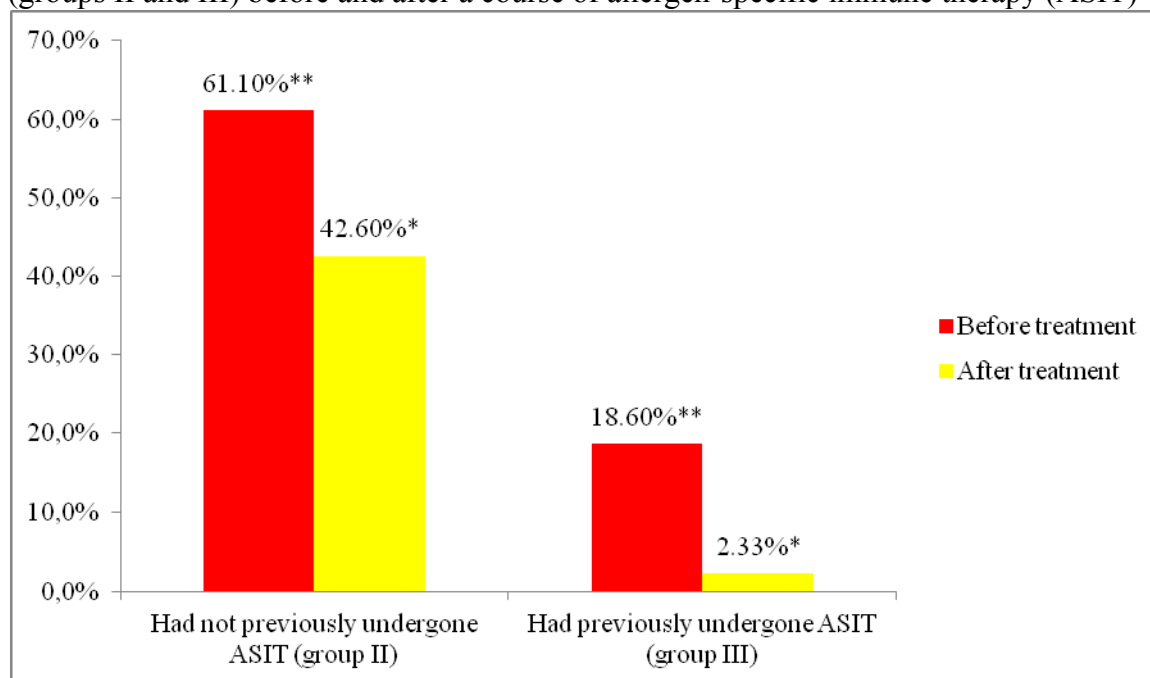
Note. The keys to structure of the complex (a, b, c) are given in the main text.

Pic. 3. Frequency of reduction in cognitive activity (CA) parameters in the children with pollinosis (before treatment)



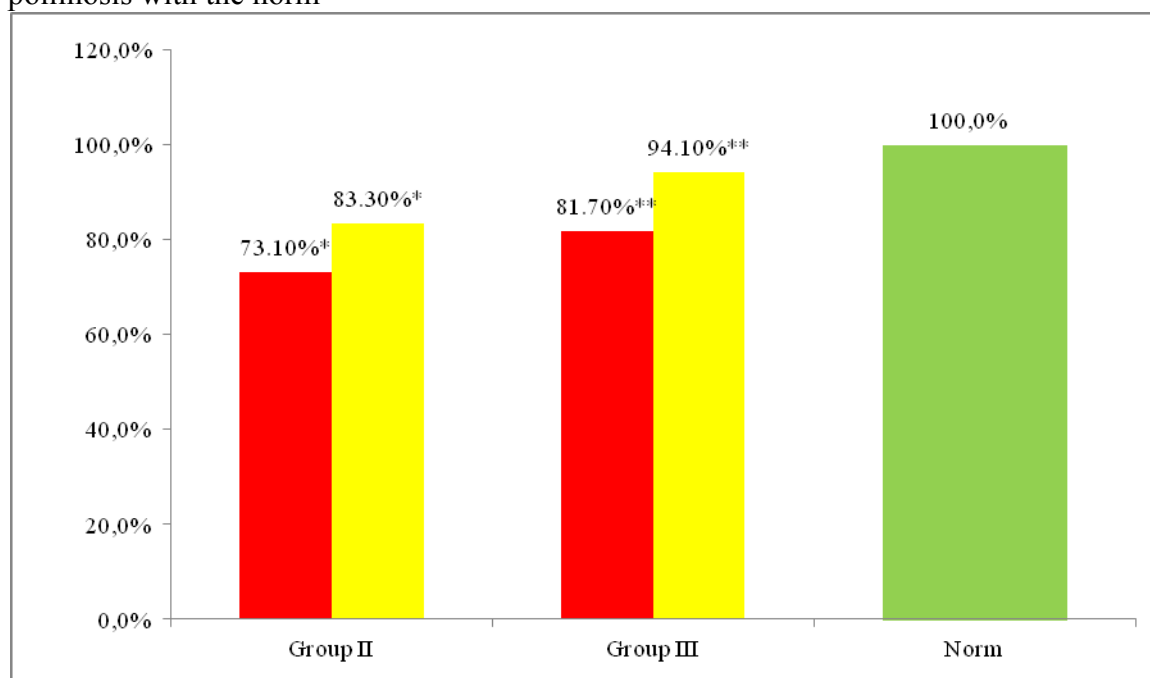
Note. * - significant differences ($p < 0.05$) between subgroups II-before and III-before regarding low CA.

Pic. 4. Rate of reduction in cognitive activity (CA) parameters in the children with pollinosis (groups II and III) before and after a course of allergen-specific immune therapy (ASIT)



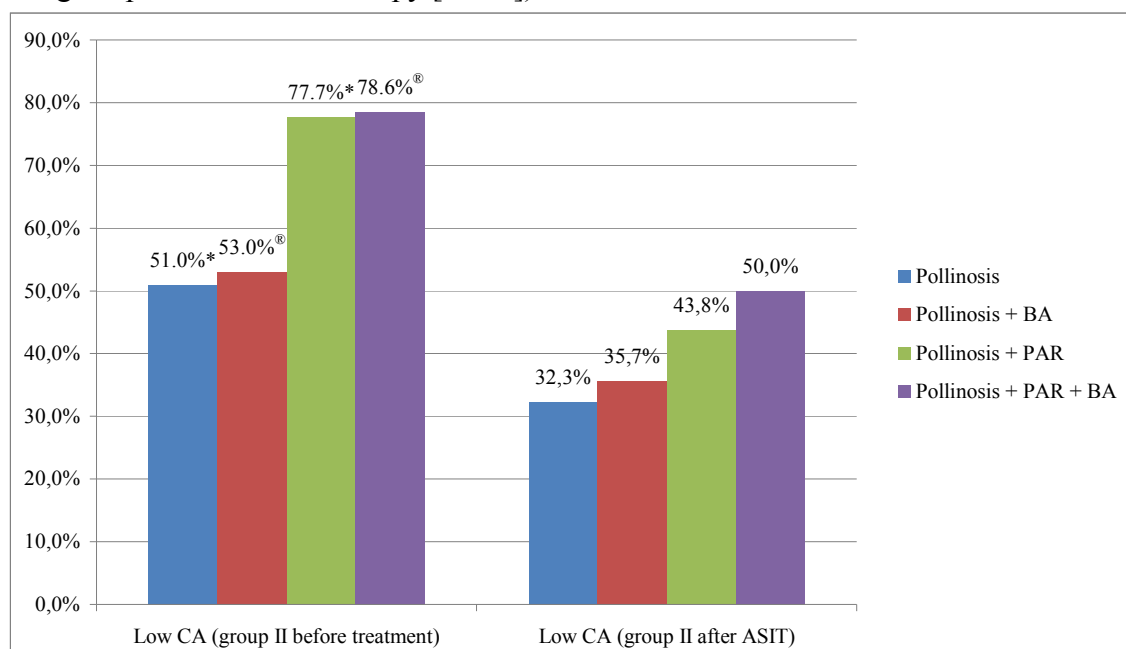
Note. * - significant differences ($p < 0.05$) between subgroups II-after and III-after.
 ** - significant differences ($p < 0.05$) between subgroups II-before and III-before.

Pic. 5. Percent correlation of the average total cognitive activity value of the patients with pollinosis with the norm



Note. * - significant differences ($p < 0.05$) between subgroups II-after and III-after.
 ** - significant differences ($p < 0.05$) between subgroups II-before and III-before.

Pic. 6. Rate of cognitive activity (CA) reduction in children with pollinosis depending on the type of concurrent allergic pathology: group II (who had not previously undergone allergen-specific immunotherapy [ASIT])



Note. * - significant differences ($p < 0.05$) in subgroup II-before: pollinosis and pollinosis + perennial (persistent) allergic rhinitis (PAR), ® - significant differences ($p < 0.05$) in subgroup II-before: pollinosis + bronchial asthma (BA) and pollinosis + PAR + BA.