O.I. Muradova[1], L.S. Namazova-Baranova[1, 2, 3], G.A. Karkashadze[1], O.I. Maslova[1], R.M. Torshkhoeva[1], A.Yu. Tomilova[1, 2], A.A. Alekseeva [1, 2], E.A. Vishneva[1], K.S. Volkov [1, 2], T.A. Konstantinidi [1]

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

[2] I.M. Sechenov First Moscow State Medical University, Russian Federation

[3] N.I. Pirogov Russian National Research Medical University, Moscow, Russian Federation

Impact of the Second Generation Antihistamines on Cognitive Function in Children with Pollen Allergy Receiving Specific Allergen Immunotherapy

Author affiliation:

Muradova Olga Islamovna, pediatrician, MD, SCCH Research Institute of Preventive Pediatrics and Rehabilitation Treatment Cognitive Pediatrics Department researcher **Address:** 119991, Moscow Lomonosov ave., 2 building 1, **tel.:** +7 (499) 134-03-92, e-mail: Muradova@nczd.ru

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Relevance*. Allergic pathology and in particular pollen allergy can lead to a decrease in cognitive functions in children. Earlier it was established that antihistamine preparations of generation I influence the cognitive functions of patients. Patients with this nosology have been receiving by now longtime courses of antihistamine preparations of II generation, so the analysis of the influence of different AH preparations of II generation on the cognitive activity of children with hay fever is necessary.* ***Purpose.*** *Studying the impact of II generation antihistamine preparations and specific allergen immunotherapy on the cognitive functions at children with hay fever.* ***Patients and methods****. The condition of cognitive functions was established using the «Psihomat» psychophysiological computer complex. In total 81 children with pollen allergy were investigated. The persons under consideration were divided into subgroups depending on the antihistamine which they received. For the patients in the main group of investigation the cognitive functions have been studied in 3 points.* ***Results****. The patients had changes in the attention and psychomotor activity more often, than in other cognitive activity. Distinct data on a vivid contribution of second generation antihistamine preparations to the improvement of cognitive activity as a whole in complex treatment of pollen allergy with specific allergen immunotherapy was not obtained. Antihistamine preparations (desloratidine and cetirizine) improve indexes of visual and space perception in children with pollen allergy. From the 3 antihistamine preparations cetirizine has the most positive effect on the psycho-motoric activity in the combined AST.* ***Conclusion.*** *Additional research is necessary for receiving definite answers to the problem questions in the field.*

***Key words**: pollen allergy, allergic rhinitis, antihistamine preparations of II generation, cognitive functions, specific allergen immu notherapy, computer psychophysiological complex «Psychomat», cognitive activity.*
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INTRODUCTION

As we know, in recent years there has been a steady growth in allergic diseases. More than 25% of children in the world suffer from various forms of allergic pathologies [1].

Hay fever (pollen allergy) is a seasonal allergic disease caused by pollen of wind-pollinated plants. Manifestations of hay fever are caused by inflammatory changes in the mucous membranes, especially in the respiratory tract and eyes, the most common of them are allergic rhinitis (AR; 95-98%) and conjunctivitis (91-95%) [2, 3]. The AR is based on IgE-dependent allergic inflammation of the nasal mucosa, mediated by a complex interaction of the effector cells and a wide range of mediators (cytokines, chemokines, neuropeptides and adhesion molecules), causing the symptoms development and disease progression, and formation of non-specific nasal hyperreactivity. One of the important allergy mediators, released from the granules of mast cells and basophils, is histamine. Its effect on the body is mediated by four types of histamine receptors (H1, H2, H3, H4). In the development of symptoms of diseases associated with hypersensitivity reactions, activation of H1 receptors is the most studied. Stimulation of H1-receptors leads to vasodilation and increase of vascular permeability, strengthening of the secretory activity of glands of the nasal mucosa, causes irritant receptor irritation, itching of skin and mucous membranes, as well as smooth muscle contraction of the bronchi and gastro-intestinal tract. Through H1-receptors, histamine takes part in chemotaxis of eosinophils and neutrophils, formation of prostanoids (prostaglandins F2α, D2, thromboxane, and prostacyclin), activates the NF-kB complex, participating in the transcription of adhesion molecules and inflammatory cytokines [4, 5]. Thus, histamine not only actively influences the rhinitis symptoms development in the early phase of the allergic reaction, but also plays an important role in the formation of persistent allergic inflammation. One of objective tasks of pharmacotherapy in the diseases treatment with the given pathogenesis link, is preventing histamine stimulation of its target organs, while the main medicines are antihistamines [6, 7].

Despite the fact that the history of using antihistamines counts decades (their use in clinical practice started in 1942), antagonists of H1-receptors remain the most important group of drugs,

used in clinical allergology up to modern days. The numerous group of antihistamines is divided into I-generation (sedative) and II-generation (nonsedative) [8].

A distinctive feature of I-generation antihistamines (antihistamines I) is a wide range of side effects, which is largely caused by their relatively low specificity for H1 and the ability to interact with other receptors (cholinergic, α-adrenergic, dopamine, and serotonin) [8, 9]. Thus, a sedative effect, drowsiness, decreased concentration, and cognitive impairments are associated with the penetration through the blood-brain barrier and the blockade of H1-receptor and M-cholinergic receptors of the central nervous system. There is a clinical delusion, when the sedative effect is treated as a positive effect of the drug, which earlier was used wrongly for the blockage of night manifestations of diseases such as bronchial asthma.

Generation I antihistamines are significantly inferior to drugs of generation II not only in the safety criteria, but also in efficiency, due to their incomplete connection with N1- receptors. As a result, there is a need of prescription of relatively high doses of antihistamines I, which leads to the development of new side effects. In addition, the short-term effect and subsequent multiple prescription of this subgroup's drugs contribute to a rapid development of tachyphylaxis – an eventual progradient decrease of the therapeutic effect and, as a consequence, the need to alternate medicines every 2-3 weeks.

Results of several clinical studies are published in scientific journals, as well as large-scale retrospective meta-analysis, confirming the low safety profile of AGP I, according to the position of evidence-based medicine [10-13]. Medicines and Healthcare Products Regulatory Agency UK recommended not to prescribe preparations containing N1-antihistamines of I generation to children younger than 6 years [14].

Compared with the I-generation drugs, histamine receptor blockers of the II generation have a number of advantages: high affinity with the H1-histamine receptors, low competitiveness of binding with them, fast effect start, sufficient duration of antihistamine effect, absence of blockade of other receptor types and absence of tachyphylaxis effect. II generation antihistamines are characterized by low lipophilicity, low penetration level across the blood-brain barrier, and a rapid removal out of the central nervous system by transport systems (P-glycoprotein et. al.) In therapeutic doses these preparations block less than 30% of central H1-receptors, do not have sedative effects and negative impacts on cognitive functions [10, 15]. Nevertheless, there are unitary literature data on the ability of individual II generation drugs to render a sedation effect, and as a result, affect the patient's cognitive function [16]. According to the Food and Drug Administration (FDA; USA), cetirizine causes drowsiness in 1,9-4,0% of cases [14, 17].

According to available data, antihistamines II, such as desloratadine, loratadine, and fexofenadine, do not have a sedative effect, do not affect concentration, memory and learning ability when used in therapeutic doses. Cetirizine and levocetirizine pass through the blood-brain barrier in a much lesser degree than antihistamines I [14]. In 2008, in Allergic Rhinitis and its Impact on Asthma Initiative (ARIA) international guidelines, it was noted that many antihistamines of the II generation are efficient and safe in the treatment of allergic rhinitis in children, but in long-term studies, such properties were confirmed only for cetirizine, levocetirizine and loratadine [17].

Thus, while there is a set of works, proving the impact of antihistamines I on the cognitive function in children, scientific studies on the impact of antihistamines II on the mental capacity remain unitary. For example, in the study of antihistamine influence on the cognitive function in children with urticarial, it was shown that fexofenadine and ebastine, being the most effective antihistamines in treatment of chronic urticaria, do not adversely affect the patient and, accordingly, can be recommended for prolonged treatment of the disease. Cetirizine, in spite of the pronounced positive therapeutic effect, reduces the attention and impairs thinking in patients with chronic urticaria. Loratadine, in contrast, has a positive effect on the attention and thinking of patients, but because of its lower efficiency can be preferred as the basic therapy of mild course of chronic urticaria [18]. In general, it should be recognized that the fragmentariness and scarcity of available data, as well as its inconsistency, do not allow to fully answer the question about the impact of antihistamines II on the children's cognitive function.

A study conducted earlier in NCCH, found that 95.3% of adolescents who had been long-suffering from persistent allergic rhinitis with year-round manifestations (of moderate and severe course), had disorders of cognitive functions, and an adequate therapy of intranasal steroids resulted in significant improvement in the studied parameters [19]. Our last work in this area was devoted to studying the cognitive functions in children with hay fever during remission. The results showed mental capacity disorders in case of hay fever in remission. Related allergic pathology in the form of broncial asthma did not have a pronounced effect on the cognitive impairment, while attaching perennial allergic rhinitis - largely worsened it. Allergen specific immunotherapy significantly improved cognitive functions in children with hay fever, in repeated courses the positive effect amplified.

Given the relevance of the problem, the purpose of the work was to additionally proccess the previous studies' results [20-22] to obtain information about a possible connection between the antihistamines intake factor and the state of cognitive functions in children with hay fever.

PATIENTS AND METHODS

Study participants

Inclusion criteria: children with a verified diagnosis of "hay fever" aged 8 to 17 years.

Exclusion criteria: lack of motivation to do tasks during the cognitive activity study.

Study participants took antihistamines together with with topical steroids during both allergen immunotherapy (ASIT), and the exacerbation of hay fever. Antihistamines were prescribed in age dosages according to indications.

The subjects were divided into groups according to the taken antihistamine. Subgroups were comparable by sex and age. Patients of subgroup I received desloratadine, subgroup II patients - levocetirizine, subgroup III patients - cetirizine; subgroup IV patients (comparison group; n = 16) did not receive any antihistamines during ASIT. The study of cognitive function occured at 3 points: 1st - hay fever in remission without treatment, 2nd – 40-45 days after the ASIT course and antihistamines intake, 3rd - during hay fever exacerbation while taking antihistamines and topical steroids.

Fig. 1. CPPC-99M complex "Psychomat"

Research methods

To quantify the cognitive function in children, we used the Psychomat computer psychophysiological complex (CPPC-99M "Psychomat"; LLC "Medproekt Vita", Russia; Fig. 1). A survey using CPPC-99M "Psychomat" consists of the following stages:

1) computerized tasks are presented through visual and auditory signals of different modality using a screen and a special control panel;

2) the examinee responds by tapping the touch-sensitive buttons on the control panel;

3) the computer program registers the answers;

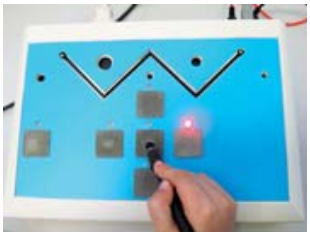
4) the results are counted, computerized and proccessed.

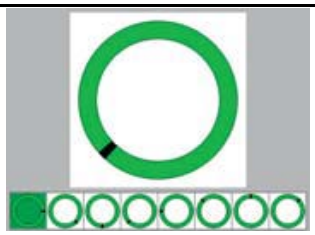
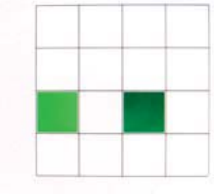
These procedures ensure the standardization and objectification of the survey with minimizing the human error factor [23].

Psychomat contains a large number of tasks. We chose a set of 6 tasks for this study on cognitive responses (Table 2).

Statistical analysis. Statistical analysis was performed by the Biostatistic program. The significance of differences in groups between values at different points was calculated using Student's t-test. Analysis of the various forms of related allergic pathology was performed using the Mann-Whitney criteria.

Table 1. Tasks selected for the research

1. Simple sensorimotor reaction: mostly fast motor response to a simple light signal. The subject is instructed to respond as quickly as possible to an emitting light signal by pressing a button. Allows to estimate the speed of simple (without selecting the reply form) sensorimotor reactions to a supplied stimulus (indicators - average motor time, average latency time)	
2. Test for static coordination: the examinee should hold the ferrule in the highlighted test hole without touching its sides and/or bottom (indicator - frequency of touches)	
3. Test for dynamic coordination: the examinee should lead the ferrule through a narrow channel in the form of a broken line, without touching its sides and bottom (indicator - integral value)	

4. Proofreading test with Landolt rings: intended for researching attention and visual space perception (indicator - the number of errors)	
5. Mnemotest: intended to assess the visual-imagery and visuospatial memory (indicator - the average number of correct answers to one light image)	
6. Binatest in controlled selection mode: the examinee should try to guess the sequence of pressing the left and right buttons on the remote control, which will be offered by the program; the ability of elementary analysis is assessed (indicator - the overall level of error)	

RESULTS

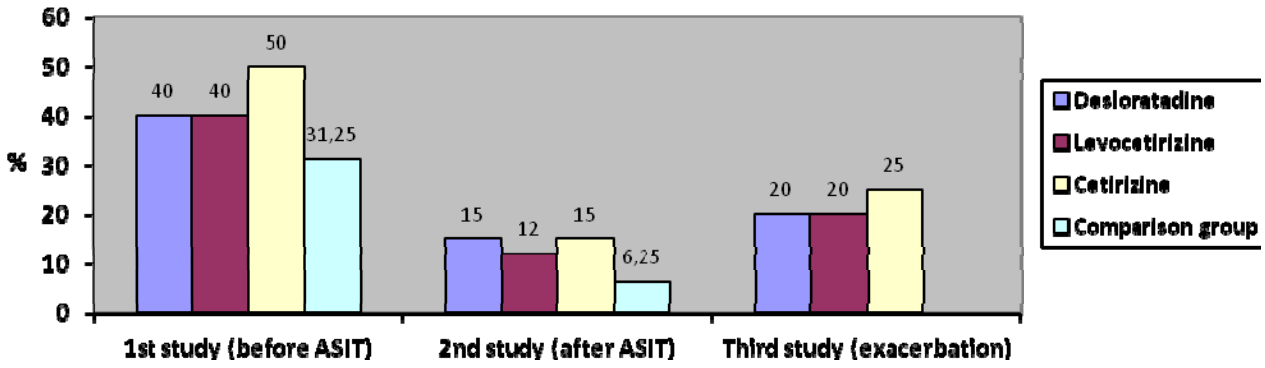
The study involved 81 people with hay fever, which manifests itself in the form of allergic rhinitis and conjunctivitis. Average age of the participants - 10.5 years. Gender composition: girls - 34 (42%), boys - 47 (58%). Control group - mentally healthy children without any allergic patholigies. Subgroup I (desloratadine) included 20 children, Subgroup II (levocetirizine) - 25, Subgroup III (cetirizine) - 20. The comparison group included 16 patients, not receiving antihistamines during ASIT.

Obtained indicators of cognitive activity (CA) of children in the groups studied were compared with those of healthy pupils. Decrease in cognitive activity was defined as indexes of 3 and more sigma less than the standard normal indexes of the control group (confidence interval) for at least in two of the six presented tasks.

It has been established that initially in almost all subgroups, the CA was reduced by 40-50% of patients. In the comparison group initially there was a smaller number of patients with cognitive functions reduction indexes (only 31.25%), which indirectly may indicate a less severe hay fever course and, accordingly, the absence of need for antihistamine therapy during ASIT. In the studied subgroups, the percentage of children with CA impairment after ASIT decreased equally (25-35%). Accordingly, we conclude that combined use of ASIT and antihistamines of the II

generation do not significantly affect the CA positive dynamics paces in patients with remission of hay fever (Fig. 2).

Fig. 2. Dynamics of the CA violations in children with hay fever depending on receiving antihistamines of the II generation



In the desloratadine group, a decline in the number of patients with impaired CA after ASIT by 25% was noted, while in the levocetirizine group this figure was 28%, and in the cetirizine group - 35%. Due to the small number of patients, differences are inauthentic, but we can talk about the trend of more pronounced positive impact of cetirizine on the CA compared to desloratadine and ASIT in control group.

In order to obtain more detailed information on the CA, we analyzed the cognitive disorders in absolute values (total severity of violations by points; Table 2). A study of cognitive functions was conducted on 16 indexes of different tests. Accordingly, normal values were in the range of ± 16 points, and the degree of cognitive functions' impairment in a patient was determined by the total coefficient of the cognitive changes degree Y_{Sum}:

$$Y_{sum} = \Sigma Yb \text{ (each parameter of each test).}$$

Table 2. The dynamics of cognitive activity of children with hay fever depending on the receiving antihistamines, estimated by total coefficient of cognitive disorders severity

Subgroups	1st study (before ASIT)	2nd study (after ASIT)	Third study (exacerbation)
	Average score		
I (n = 20) desloratadine	-16.2	-2.8	-5.1
II (n = 25)	-10.2	-2.5	-2,72

levocetirizine			
III (n = 20) cetirizine	-12.97	-1.65	-1.71
IV (n = 16) comparison group	-11.9	-1.84	-2.9

Note. Here and in tables 3-6: ASIT - allergen specific immunotherapy.

This analysis demonstrated a greater efficiency of the CA improvement in desloratidine (+13.4) and cetirizine (+11.32) compared with levocetirizine (+7.7 points; p <0,05). On the other hand, while taking desloratadine during the exacerbation of hay fever, the average CA index has worsened compared to the previous study level (after ASIT in remission); thus, it can be assumed that the given antihistamine is not sufficiently effective in this group of patients relative to the stabilization of the CA .

Analysis of the antihistamines II effect on separate blocks of cognitive functions was carried out in the work.

Table 3. *Dynamics of psychomotor activity violations in children with hay fever, depending on the receiving antihistamines*

Groups	1st study (before ASIT)	2nd study (after ASIT)	Third study (exacerbation)
	Cognitive activity below normal,%		
I (n = 20) desloratadine	45	15	40
II (n = 25) levocetirizine	28	20	24
III (n = 20) cetirizine	35	25	15
IV (n = 16) comparison group	18.75	6.25	-

Psychomotor activity block

In the subgroup of desloratadine, the most pronounced effect of reducing the number of children with psychomotor activity violation was marked after combined therapy with ASIT (30% versus 8 and 10 - in other antihistamine subgroups, and 12% - in the control group; p <0,05). But on the other hand, in the spring - during the exacerbation of hay fever - the actual return to pre-treatment indicators was characterizing for this group (Table 3). In this case, it would be possible to

say that desloratadine is more effective than other antihistamines in psychomotor functions improving as a part of combined therapy with ASIT, but its positive effects are less persistent, if there are no the following methodological limitations.

Table 4. *Dynamics of voluntary attention violations in children with hay fever, depending on the receiving antihistamines*

Groups	1st study (before ASIT)	2nd study (after ASIT)	Third study (exacerbation)
	Cognitive activity below normal,%		
I (n = 20) desloratadine	55	thirty	thirty
II (n = 25) levocetirizine	52	24	28
III (n = 20) cetirizine	45	20	25
IV (n = 16) comparison group	18.75	6.25	-

Table 5. *Dynamics of the visuospatial perception violations in children with hay fever, depending on the receiving antihistamines*

Groups	1st study (before ASIT)	2nd study (after ASIT)	Third study (exacerbation)
	Cognitive activity below normal,%		
I (n = 20) desloratadine	45	15	25
II (n = 25) levocetirizine	12	4	16
III (n = 20) cetirizine	40	20	20
IV (n = 16) comparison group	12.5	12.5	-

An interesting regularity for cetirizine is established: although in its subgroup, psychomotor activity after a combined treatment improved more rarely than in desloratadine and comparison subgroups, but this improvement demonstrated a positive dynamics, and in the future resulted in the

minimum value of frequency of psychomotor activity violations during the seasonal exacerbation of hay fever - 15%. Thus, the ultimate positive dynamics of reducing the psychomotor activity violations number from the 1st to the 3rd study in the subgroup of cetirizine had left 20% in contrast to 5 and 4% for other antihistamine subgroups ($p < 0.05$). Perhaps cetirizine makes a greater contribution to the improvement of psychomotor activities for a long time due to the prolonged effect in the combined treatment period among three antihistamines.

Voluntary attention block

Violations of voluntary attention were fixed more often than other cognitive disorders. The dynamics of voluntary attention violations in the 2nd and 3rd points of the study were comparable for all three antihistamines (table 4).

Visual-spatial perception block

In all three antihistamines (particularly in cetirizine and desloratadine) there was a significant improvement in visual-spatial perception immediately after the ASIT course compared with the comparison group (30.8 and 20 vs. 0%, respectively; $p < 0,05$; table 5). Apparently, we can talk about the contribution of antihistamines to improving the visual-spatial perception function in children with hay fever.

A trend, previously defined for the psychomotor activity block, was also noted in this block: in the desloratadine subgroup, immediately after ASIT, cognitive functions improved more often than in the cetirizine subgroup, but were prolonged; taking into account the period of exacerbation, the improvement in visual-spatial perception in these subgroups is the same.

Table 6. *Dynamics of the visuospatial memory violation in children with hay fever, depending on the receiving antihistamines in points*

Groups	1st study (before ASIT)	2nd study (after ASIT)	Third study (exacerbation)
	Cognitive activity below normal,%		
I (n = 20) desloratadine	40	thirty	40
II (n = 25) levocetirizine	24	16	20
III (n = 20) cetirizine	25	10	20
IV (n = 16) comparison group	18.75	6.25	-

Visual-spatial memory block

Positive dynamics in this kind of cognitive activity were recorded more rarely than in other types of CA (table 6).

The dynamics of visual-spatial memory violations in the 2nd and 3rd points of the study were comparable in all three antihistamines subgroups and in the comparison group. Thus, there are no obtained evidences in favor of antihistamines contributing to the improvement of visuospatial memory in combined therapy with ASIT. No adverse effects of therapy were observed.

DISCUSSION

The specifics of the study, which initially was not planned as investigating the effect of antihistamines on cognitive activity, imposes a number of restrictions on interpretating the results and conclusions. Firstly, it is the absence of "clear" groups where antihistamines would be used as the only treatment. Secondly, it is the possible clinical heterogeneity of subgroups. In particular, in the levocetirizine subgroup, the severity of cognitive impairment was initially the lowest, which could provide less pronounced positive dynamics of this drug. Conversely, in the cetirizine subgroup, cognitive impairment was more common, which could affect the best indicators of positive dynamics. Violation of the psychomotor activity was most frequently mentioned in the desloratadine subgroup: accordingly, it could contribute to a better positive trend in children taking it. A third limitation - insufficient number of observations for the condition of "unclear" groups. In connection with the above, not all observed differences in the cognitive effects of antihistamines "flow" in the obvious conclusions, but they are estimated with a fair degree of conditionality.

Though we are talking about the effect of antihistamines on the cognitive activity of the child with hay fever as about a certain one-piece phenomenon, it should be borne in mind that such effect can contain two oppositely directed mechanisms:

1) the well-known effect of CA oppression by antihistamines (known by first-generation drugs);

2) the ability to improve the CA, which was previously impaired by hay fever, as a consequence of the overall positive therapeutic effect against hay fever (as it was demonstrated earlier for ASIT) [16, 17].

The methodology of this study allows to evaluate only the overall final effect of antihistamines II together with ASIT treatment of children with hay fever, but it does not allow to judge the contribution to the total effect of each of the above constituents.

If we talk about the overall impact on cognitive activity, it can be assumed with a certain degree of conditionality that the accession to ASIT of three popular antihistamines in general does not affect the rate of CA improvement in children with hay fever.

Cetirizine enhances the overall positive effect on the CA after ASIT, but does not retain this advantage for the seasonal exacerbation of hay fever.

Tendencies, found in the analysis of the antihistamines impact on the separate blocks of cognitive impairment, look more distinctive. Apparently, antihistamines (particularly cetirizine and desloratadine) improve the visual-spatial perception indications in children with hay fever. This could be explained by the fact that antihistamines' own sedative effect is primarily concerned with the dynamic functions associated with attention, speed of psychomotor processes and memory, to a lesser extent affecting the quality of perception, thinking, praxis and speech. If assumed that the final cognitive effect contributes to the antihistamine sedative effect, it becomes clear why visual-spatial perception indexes are better than those of voluntary attention, psychomotor performance and memory: in the first case we are talking about stable quality characteristics, not suffering from the sedation effect, and in the second - about neurodynamic processes, more sensitive to the sedative effect. In relation to other cognitive functions, no significant differences from the control group were revealed.

When comparing antihistamines with each other by the impact on psychomotor functions and visual-spatial perception, we revealed tendencies to greater effectiveness of desloratadine in the improvement of these two function blocks immediately after combined treatment with ASIT and the comparative instability of these improvements after hay fever exacerbation, as well as to more prolonged effectiveness of cetirizine all the way up to hay fever exacerbation.

FINDINGS

1. Detalization of cognitive impairment during hay fever in remission showed that voluntary attention and psychomotor activity are more often violated in patients.

2. No distinct data was obtained about II generation antihistamines' own contribution to the improvement of cognitive activity when used together with ASIT treatment for hay fever.

3. Antihistamines cetirizine and desloratadine improve visual-spatial perception indications in children with hay fever. Perhaps this is due to the absence of their sedative effect on this kind of cognitive activity.

4. Cetirizine has the best prolonged positive effect in relation to psychomotor activity in combination with ASIT therapy among the three antihistamines.

5. With regard to impact on psychomotor activity and visual-spatial perception, desloratadine and cetirizine have different dynamic characteristics: desloratadine has a peak profile with maximum effect immediately after therapy with ASIT and a recession during hay fever exacerbation, while cetirizine has a flatter profile.

CONCLUSION

The influence of II generation antihistamines on the cognitive activity of children is still a problem in worldwide pediatrics. The results of this study do not allow to judge conclusively the ultimate impact of antihistamines on the cognitive activity of children, but show differences in the dynamic profile of their impact and in the specifics of inner-cognitive effects. This demonstrates the need for further studying the issue in the form of special studies.

CONFLICT OF INTEREST

The authors have indicated they have no financial support / conflict of interest relevant to this article to disclose.

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