## M.V. Ryazanov<sup>1</sup>, L.S. Namazova-Baranova<sup>1,2,3</sup>, A.G. Nadtochii<sup>4</sup>

<sup>1</sup>Scientific Centre of Children's Health, RAMS, Moscow

<sup>2</sup> I.M. Sechenov First Moscow State Medical University

<sup>3</sup> N.I. Pirogov Russian National Research Medical University, Moscow

<sup>4</sup> FGBU Central Scientific and Research Institute of Dentistry and Maxillofacial Surgery of Ministry of Health and Social development of Russian Federation, Moscow

# Assessing the Effectiveness of Allergen Immunotherapy in Children With Seasonal Asthma Using Doppler Studies on Major Salivary and the Thyroid Glands

### **Contact data:**

*Ryazanov Mikhail Valeryevich*, Head of Department of ultrasound research of Institute of Preventive Pediatrics and Rehabilitation SCoCH, RAMS

Address: 119991, Moscow, Lomonosovsky ave., 2/2 phone: (495) 967–14-20

Received: 05.12.2011, accepted for publication: 01.03.2012

The article is concerned with the capabilities of ultrasound diagnostics as an additional effectiveness criteria of various methods of introducing allergens to children with seasonal asthma in remission during allergen immunotherapy (ASIT). For the first time the dynamics of parenchymal blood flow of salivary glands were evaluated during allergen immunotherapy. It was established that during ASIT the parenchymal blood flow is activated. It is shown that pathogenetically substantiated therapy leads to improvement, which is echographically expressed by normalization of hemodynamics of intraorganic vessels.

**Keywords**: allergen immunotherapy, asthma, diagnosis, children, Doppler, salivary gland, ultrasound, thyroid gland.

Bronchial asthma (BA) is a common child disease. Development of pollen asthma can be caused by allergens of three major groups of plants: trees and shrubs, grasses, weeds [1]. According to data from the literature of recent years, allergen immunotherapy (ASIT) is the only known treatment that can alter the natural course of allergic disease. After ASIT conduction effect is presented by long-term remission, prevention of disease progression and expansion of the spectrum of cause-significant allergens, as well as by decrease in dosage of drugs used for basic treatment, thereby reducing the cost of further treatment [2].

Currently there is actively discussed ASIT implementation through such non-invasive methods as sublingual and endonasal. Sufficiently high effectiveness of these treatments is associated with the light absorbability of allergens from the nasal mucosa, oral cavity and their rapid penetration into the regionar lymph system [3].

The study of the salivary glands currently attracts more attention of scientists and physicians of various specialties. The study of this organ (including ultrasound) has several advantages in comparison with other routine methods of laboratory diagnosis, especially on blood, given the prevalence of infectious diseases (HIV, hepatitis, etc.): simplicity and accessibility of the method for a child of any age without any negative effects; it is non-invasive and painless, has no risk of infection, there is possibility of multiple introduction. Anatomy specialties of the salivary glands, and their superficial location, features of mouth floor, being an active suction of the adsorbing membrane, is widely used in clinical practice for studying the pharmacodynamics of drugs [4]. The aim of this work was to study the ultrasound diagnosis as an additional criterion effectiveness of various methods of introducing allergens in children having hay fever during the period of ASIT remission.

#### **Patients and methods**

The work was conducted at the Department of ultrasound and rehabilitation of children having allergic diseases of Institute of Preventive Pediatrics and Rehabilitation of CHSC, RAMS. To achieve the objectives there were examined 200 children: 40 healthy children as a comparison group and 160 children aged 5 - 17 years with hay fever during the remission period.

The primary group of children having allergic diseases, who received ASIT, consisted of 160 patients aged 5 - 17 years. The primary group was divided into four equal subgroups according to the method of ASIT: subcutaneous (SC), sublingual (SL), combined (KMB) and endonasal (EN). The comparison group consisted of 40 children correspinding sex and age, anf having no allergic disease.

In each sub-group there was noted predominance of males. In the control group the ratio was similar. The average age in the subgroups of patients was  $10.4 \pm 2.9$  years. No significant differences in or between any age groups were found.

The average disease duration was 7.2 years. Food allergy was observed in 79% of patients. Family history of allergic disease was diagnosed in 67% of patients, of whom it was diagnosed through maternal line - in 36%, on the paternal side - at 26%, through both of their parents - at 6%. In 57% of patients there was revealed polyvalent sensitization, and monovalent sensitization was revealed in 43% of patients.

On admission to the department a comprehensive survey was conducted on all patients. It included a general clinical assessment (determination of mass and body length, blood count, urinalysis), assessment of respiratory function, chest x-ray, electrocardiogram, allergy assessment (collection of allergic history data, skin scarificating trials with allergens, determination of the level of total IgE), immunological assessment (levels of immunoglobulin classes a, M, G).

For all the surveyed children there was performed echography on the ultrasound machine «Voluson 730 expert» using multifrequent linear transducer with a frequency of 10-16 MHz by polypositioned scanning of major salivary glands in the B-mode, followed by the application of color and power doppler mapping in combination with impulse dopplerography in the following sequence: parotid gland, submandibular gland, sublingual gland; there was assessed the intensity of blood flow with the following determination of the resistance index of parenchymal vessels.

The most information on the structure of the gland was received during ultrasound in Bmode. The next stage of research is the use of color and power doppler mapping to determine the vascular component of the gland, and then impulse dopplerography to assess the hemodynamics of parenchymal vessels.

In order to eliminate false results due to the fact that there is a large number of major arteries in the salivary gland, there were evaluated only small parenchymal vessels with blood flow up to 7-10 cm / s maximum, which requires placing the scale on the color doppler of not more than 3-5 cm / s. Parenchymal blood flow parameters were evaluated: peak systolic velocity (PSV, cm / s), end diastolic velocity (EDV, cm / s), resistance index (RI), systolic-diastolic ratio (S / D). The degree of vascularization of the salivary gland before and after therapy was assessed subjectively by the number of color pixels. During color doppler mapping there could be observed intense color signals with the multidirectional movement of blood flow.

The thyroid gland was studied twice in each patient according to standard procedure - estimation of the total thyroid volume, and of parenchymal hemodynamics indices.

Statistical analysis of the results of the study was conducted using the data analysis package Microsoft Office Excel 2003 and Statistica 6.0. In the analysis of small samples, that do not obey the normal distribution, there was calculated Mann-Whitney criterion for unpaired comparisons, and Wilcoxon criterion for paired comparisons. Multiple comparisons were performed using Kruskal-Wallis and Duncan test criteria. The significant differences were considered at p <0,05.

#### **Results and discussion**

At the first stage there was assessed the state of blood flow in major salivary glands and thyroid gland in children having allergic diseases before ASIT, and there was effected a comparison with a group of healthy children.

No significant differences were found in the subgroup of patients treated with ASIT by subcutaneous injection (p> 0.05); blood flow to the right and left large salivary glands was

symmetrical. Blood flow was not determined in the sublingual gland, because of the anatomical features of its location. Resistance index in this subgroup of patients was below normal values (0,6-0,69 according to the special literature) as a whole prior the treatment.

In the subgroup, which received ASIT treatment by sublingual method, it was discovered that such blood flow indicators, as resistance index and systolic-diastolic ratio, were slightly higher in the left parotid gland (p <0.05). Blood flow was not determined in the sublingual gland in the same way as in the previous subgroup. The values of resistance index in the salivary glands reached lower limit of normal (0.5-0.6).

According to a survey of patients treated with ASIT using combined method (subcutaneous + sublingual), it was found that before treatment this subgroup had higher rates of blood flow in the right parotid gland compared with the left on almost all criteria (p < 0.05), and other glands revealed no differences. The values of resistance index in the salivary glands weer located on the lower limit of normal (0.6).

In group of patients treated with endonasal technique, there were revealed higher values of peak systolic blood flow velocity in the right parotid and submandibular glands compared with the left (p <0.05); there were established no significant differences on other indicators. Blood flow in the sublingual glands was not determined. Resistance index was below normal values (0.5-0.6).

There were found no significant differences in blood flow of large salivary gland in children from comparison group. It was noted that in contrast to children having allergic disease, blood flow in the sublingual glands of healthy children was determined. Resistance index was within standard values - 0.6-0.7.

Therefore, the study of blood flow before ASIT start showed that differences in ultrasound parameters between subgroups of children in the intervention group were insignificant. In the study group, blood flow in the thyroid gland was significantly higher than in the salivary glands. Patients having allergic disease, had significantly lower rates of blood flow before ASIT in almost all major salivary glands in comparison with healthy children.

The next step of this research was studying blood flow in major salivary glands and thyroid gland after ASIT. It should be noted that the general trend for all subgroups, except for the subgroup of patients in which endonasal method of allergen administration was chosen, was to determine the presence of blood flow in the sublingual gland; and at the same time, the blood flow in the thyroid gland did not have any dynamics after the performed treatment.

Comparative analysis of blood flow parameters in the right parotid gland showed significant differences between groups on PSV (p = 0.005), EDV (p = 0.009), IR (p = 0.001) and

S / D (p = 0.002) (Fig. 1). The highest results on the criteria of peak systolic and end diastolic velocity were obtained using the sublingual ASIT method.

In the left parotid gland there was discovered quite a difference between the blood flow in groups on PSV (p <0,001), EDV (p = 0,004), IR (p <0.001) and S / D (p <0.001). The differences were due to higher values of PSV and EDV in the subgroup of patients treated with sublingual method, and lower ones in the subgroup treated using endonasal technique.

Comparative analysis revealed the significant differences between groups according to the criteria of blood flow in the right submandibular gland - PSV (p <0,001), EDV (p <0,001), IR (p <0,05), S / D (p <0.005).

It was found that the highest values of peak systolic and end diastolic velocity were observed in "sublingual" subgroup, and the lowest were observed in "combinated" group.

A detailed analysis of the distribution of the mean values of IR and S / D showed that in children treated with sublingual method of introducing allergens, these parameters were higher than in other subgroups, and did not differ from the parameters of healthy children.

Comparative analysis of blood flow in the sublingual glands showed that children who received ASIT by sublingual method had the best results after treatment.

The comparison showed that statistically significant differences were determined for all parameters of the right sublingual gland blood flow: PSV (p < 0,001), EDV (p < 0,001), IR (p < 0,001), S / D (p < 0.001) (Fig. 2). They were due to the lowest values of all parameters in a subgroup that received endonasal treatment, and due to the highest ones in the subgroup that received sublingual treatment. According to several criteria, results of subgroup of combination therapy were comparable with that of "sublingual" subgroup.

During the analysis of blood flow in the left sublingual gland (Fig. 3) there were determined reliable between-group differences on all parameters: PSV (p < 0,001), EDV (p < 0,001), IR (p < 0,001), S / D (p < 0.001). The differences on PSV and EDV parameters are due to higher values in the subgroup of children treated with sublingual administration of allergens method and with the combined method, and lower values in the subgroup that received treatment through endonasal method. Patients of sublingual subgroup had the highest IR and S / D results, and patients from endonasal subgroup had minimum results.

Therefore, as a result of the study, according to the dopplerography assessment it was established that method of sublingual ASIT introduction is the most efficient and optimal one, while subcutaneous and combined methods are less effective, and endonasal method has almost no effect.

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Fig. 1. Blood flow in the right parotid gland in the compared subgroups after ASIT



Note: SC – subcutaneous administration, SL - sublingual administration, KMB - a combination of PC + SL, EN - endonasal administration; PSV - peak systolic velocity (cm / s), EDV - end diastolic velocity (cm / s), RI-resistance index , S / D - systolic-diastolic ratio.

Fig. 2. Blood flow in the right sublingual gland in the compared subgroups after ASIT



Note: SC – subcutaneous administration, SL - sublingual administration, KMB - a combination of PC + SL, EN - endonasal administration; PSV - peak systolic velocity (cm / s), EDV - end diastolic velocity (cm / s), RI-resistance index , S / D - systolic-diastolic ratio.



Fig. 3. Blood flow in the left sublingual gland in the compared subgroups after ASIT

Note: SC – subcutaneous administration, SL - sublingual administration, KMB - a combination of PC + SL, EN - endonasal administration; PSV - peak systolic velocity (cm / s), EDV - end diastolic velocity (cm / s), RI-resistance index , S / D - systolic-diastolic ratio.