

Impact of Allergic Rhinitis on Nasal Mucociliary Clearance Time in Children

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Keywords

Mucociliary clearance · Allergic rhinitis · Children · Vitamin D · Eosinophilia

Abstract

Background: Mucociliary clearance is one of the most important protective functions of the airway. Previous studies, checking the influence of allergic rhinitis (AR) on mucociliary clearance time (MCT), were made on small patient groups and brought contradictive results. **Objectives:** The aim of the study is to confirm whether AR in children influences MCT. **Methods:** The examined group consisted of 842 AR children. A total of 96 children with no history of allergy rhinitis served as a comparative group. All patients underwent saccharin and skin prick tests and tests for blood eosinophilia, nasal eosinophilia, vitamin D3 serum concentration, total and specific IgE serum concentration. **Results:** Nasal MCT was significantly longer in AR patients (mean $\pm$ SD: 10.5 $\pm$ 5.65 min) compared to controls (mean $\pm$ SD: 7.25 $\pm$ 4.3 min). Percentage of eosinophils in nasal smears in patients was significantly higher compared to controls and a weak, but significant positive correlation was observed between the percentage and MCT ($r > 0.10$, $p < 0.008$). Patients with

intermittent and persistent moderate/ severe AR had significantly longer MCT and higher eosinophilia in nasal smears compared both to patients with intermittent and persistent mild RA and controls. No correlation was observed between MCT and: participant's age, total serum IgE, vitamin D3 serum concentration, absolute number or percentage of eosinophils in blood, prick test results or duration of illness. **Conclusions:** AR affects the mucociliary clearance in children, and its deterioration is related to more severe rhinitis with higher intensity of local nasal inflammation, reflected in nasal smear eosinophilia.

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Introduction

Mucociliary clearance is one of the most important protective functions of the airway. It enables the correct functioning of nasal mucosa and protects against air pollution. Efficient mucociliary clearance requires correct functioning of the cilia and quantity of mucus. In 4–15

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year-old healthy children, the typical nasal mucociliary clearance time (MCT) varies from 5.7 to 8.2 (± 2.6) min [1, 2]. Mucociliary dysfunctions, such as primary ciliary dyskinesia, usually result in upper and lower airway diseases [3, 4] and *vice versa*: some airway disorders affect the MCT, thus resulting in the deterioration of airway function. Sinusitis or smoking in adults significantly lengthens the MCT [5]. Adenoid hyperplasia in children also significantly affects mucociliary function, and its degree negatively correlates with mucociliary capacity; however, a significant improvement in MCT is usually observed following surgical correction [2, 6]. Improvements in mucociliary function have also been noted in adult patients after quitting smoking [7].

A study based on a large group of healthy 11–90-year-old volunteers identified a significant lengthening of MCT and some structural defects in cilia in those aged over 40 [8]. These results suggest that a diminution of mucociliary function is responsible for the higher incidence of upper respiratory infection in the elderly, despite some evidence to the contrary [9].

Mucociliary clearance in the nasal mucus membrane is a very important mechanism of removing allergens in allergic rhinitis (AR) patients; however, some authors have reported significantly longer MCT in AR adults than in healthy volunteers, and it is not clear whether the patients indeed present any such mucociliary disorder [2, 10, 11]. In addition, MCT correlates well with illness duration [5], and a positive correlation has been found between MCT and the intensity of the wheal and flare reaction to house dust mites, cockroaches, and grass. [12]. In contrast, no significant differences in MCT were found between healthy subjects and AR or asthmatic patients in a study of a large group of children aged 11–14 years [13].

In addition to the uncertainty about the effect of allergy on mucociliary function, there has also been some concern about the effect of steroid treatment on MCT in adult AR patients [14]. Nevertheless, marked improvements in MCT have been observed following long-term topical steroid treatment in AR children [15], or after 1 year of allergen immunotherapy in AR patients [16].

Aim of the Study

The aim of the study is to confirm whether AR in children influences MCT and whether MCT correlates with the clinical picture of AR, patient age, disease duration, total and specific IgE level, skin prick tests wheal size, vitamin D3 serum concentration, and eosinophilia in peripheral blood and nasal smears.

Materials and Methods

The examined group consisted of 842 children with AR (age 9.5 ± 3.7 years, 405 boys and 437 girls) diagnosed in the Allergy Department of the Voivodship Rehabilitation Hospital for Children in Ameryka.

The children presented varying intensities of symptoms, times of first occurrence of AR and histories of medical treatments. The patients were divided into 4 ARIA classes based on a score for AR according to ARIA 2008 update [17]. A total of 255 patients presented intermittent mild AR, 172 persistent mild, 105 intermittent moderate/severe, and 310 persistent moderate/severe AR.

A total of 432 AR patients were monosensitized and 410 multisensitized on the grounds of the skin prick tests and sIgE measurement results. In total, 398 AR children had been treated before the study by oral anti-histamines, nasal steroids, a leukotriene receptor antagonist (montelukast) or combination of medicines. The children were examined for at least 14 days after the scheduled discontinuation of the anti-allergic drugs.

Ninety six children with no history of chronic/AR or any allergic diseases and presented with no signs of any abnormalities in laryngological examination (age 9.54 ± 3.8 , 55 girls and 41 boys) treated in the Rehabilitation Department of our hospital for posture defects served as a comparative group. During the course of the study, all patients underwent saccharin tests, as well as interviews, physical examinations, anterior rhinoscopy, basic blood analysis and tests for parasites in stools.

Children with any anatomical abnormalities to the airways, such as septal deviation, nasal or sinus polyps, adenoid hyperplasia, exposed to passive smoking, were excluded from the study, as were those with infections, chronic systemic diseases like diabetes or cystic fibrosis.

Blood Eosinophilia

The percentage of eosinophils and their absolute number per mm^3 in peripheral blood were determined microscopically in all AR children.

Nasal Eosinophilia

All AR children and 30 out of the whole comparative group of children underwent nasal mucosa smear examinations. Nasal smear was collected by swab scraping the medial surface of the inferior turbinate. The material was spread on a glass slide, fixed with cytologic fixative, then stained with May-Grunwald-Giemsa stain and observed under an optical microscope. The eosinophil count was performed on 10 immersion microscope fields (1,000) and expressed as a percentage over the cell count total.

Vitamin D3 Serum Concentration

The serum of the AR children was assayed for vitamin D3 (25[OH]D3) concentration by electrochemiluminescence using a Roche Cobas e601 analyzer.

Total IgE Serum Concentrations

Similarly, the serum of the AR children were tested for total IgE concentration. The analyses were performed by using Elecsys IgE II Immunoassay (Roche Diagnostics GmbH, Germany).

Skin Prick Tests

AR children were subjected to skin prick tests with common allergens: tree I (*Alnus glutinosa*, *Corylus avellana*, *Ulmus scabra*, *Salix caprea*, *Populus* sp.), tree II (*Betula alba*, *Fagus sylvatica*, *Quercus robur*, *Platanus orientalis*), grass (*Holcus lanatus*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, *Festuca pratensis*, *Secale cereale*), weeds (*Plantago lanceolata*, *Artemisia vulgaris*, *Urtica dioica*, *Taraxacum vulgare*), house dust mites (*Dermatophagoides farinae*, *D. pteronyssinus*), *Alternaria tenuis*, *Aspergillus fumigatus*. Tests were performed with Allergopharma (Germany) reagents.

Specific IgE Serum Concentrations

Polychex® tests (Germany) were used to assay the serum taken from AR children for specific serum IgE levels against common allergens: *Corylus avellana*, *Alnus glutinosa*, *Betula alba*, *Quercus robur*, *Phleum pratense*, *Plantago lanceolata*, *Artemisia vulgaris*, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Penicillium notatum*, *Alternaria tenuis*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Canis familiaris*, *Felis domesticus*.

Nasal MCT

All children underwent saccharine tests according to Andersen, with modifications by Ruthland and Cole [18, 19].

Before the test, all patients are asked to sit straight, to hold their breath while the mixture is placed in the nasal cavity and to indicate when they notice a sweet taste. The children are asked not to sniff, sneeze, eat or drink during the test. They are asked to swallow every 30 seconds and to report any change in taste.

A mixture comprising 2/3 of saccharine and 1/3 of medical charcoal powder was placed in the nasal lower turbinate. The charcoal component is particularly suitable for studies on children, because they do not accurately determine the moment of sweet taste perception. The nurse checked the posterior throat wall at the start of the test and then every 5 min until the moment of charcoal detection or when the child reported a sweet taste. The time elapsed from the start of the test was recorded.

Statistics

Statistical analyses were performed by using PQStat software. The significance of differences between groups was determined using the Mann-Whitney U test. Relationships between measurements and the MCT were determined using Spearman's correlation tests. A probability value (p value) <0.05 was considered statistically significant.

Results

The children age did not differ ($p = 0.502$) between examined (mean 9.54 ± 3.8) and the control groups (mean 9.81 ± 3.8).

The following results were noted in the examined group:

Nasal eosinophilia (percentage) – median – 3, 25–75%: 2–4, blood eosinophilia (percentage) – median – 4, 25–

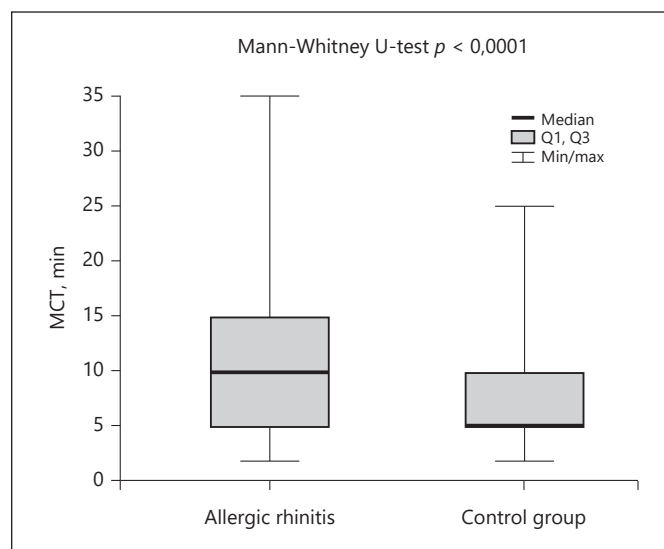


Fig. 1. Nasal MCT in children with AR and in those without AR. MCT, mucociliary clearance time; AR, allergic rhinitis.

75%: 3–5, blood eosinophilia (absolute number/ μ L) – median – 135, 25–75%: 83.7–229.3, vitamin D3 blood concentration (ng/mL, mean $\pm$ SD) – 24.6 ± 9.5 , time since the first AR symptoms (months, mean $\pm$ SD) – 39.4 ± 21.3 .

All children executed the saccharin tests well. Nasal MCT was significantly longer in the AR patients (mean $\pm$ SD: 10.5 ± 5.65 min, median: 10, 25–75%: 5–15) compared to the healthy group (mean $\pm$ SD: 7.25 ± 4.3 min, median: 5, 25–75%: 5–10), $p < 0.0001$ (Fig. 1).

MCT in children sensitized to different types of allergens did not differ between groups but was significantly longer compared to the control group. Data are shown in Table 1.

There were no difference in nasal MCT between monosensitized AR patients (median: 10, 25–75%: 5–15, mean 10.22 ± 5.7 min) and multisensitized (median: 10, 25–75%: 5–15, mean 10.05 ± 5.5 min).

MCT in AR patients was related to the clinical picture of the disease. Patients with intermittent and persistent moderate/severe AR had significantly longer MCT compared to intermittent and persistent mild AR.

Results for groups:

Intermittent mild – median: 5, 25–75%: 5–10, mean 8.78 ± 5.3 , persistent mild – median: 5, 25–75%: 5–10, mean 9.66 ± 5.2 , intermittent moderate/severe – median: 10, 25–75%: 5–15, mean 11.98 ± 6.3 , persistent moderate/severe – median: 10, 25–75%: 5–15, mean 11.52 ± 5.9 (Fig. 2).

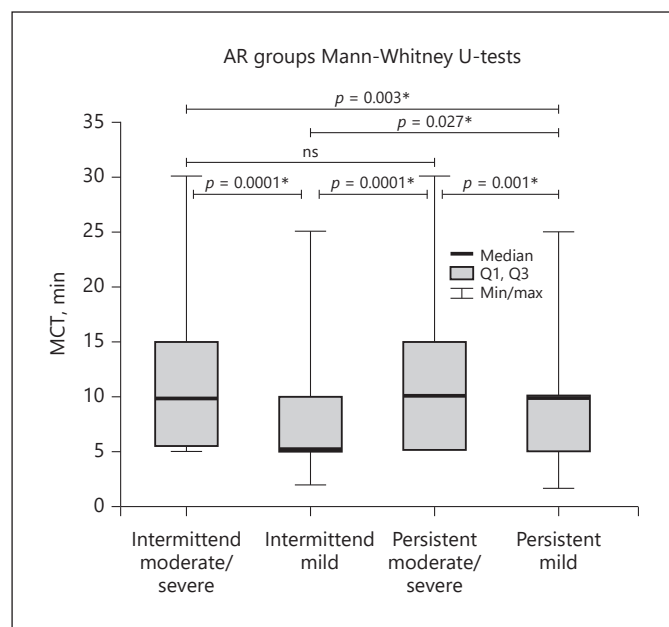


Fig. 2. Nasal MCT in AR patient groups divided into 4 ARIA classes. MCT, mucociliary clearance time.

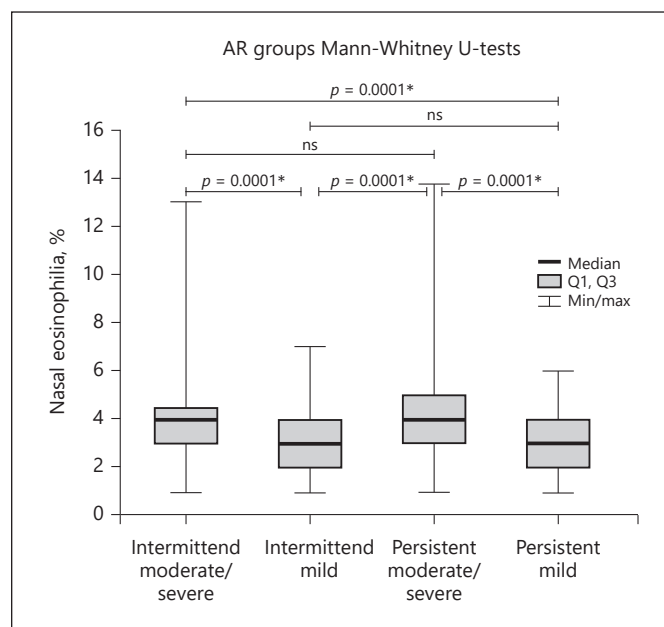


Fig. 3. Nasal eosinophilia in AR patient groups divided into 4 ARIA classes.

Table 1. Nasal mucociliary clearance times in groups of children depending on the type of sensitization (positive specific IgE or skin prick tests to the allergen)

Allergen	Mean $\pm$ SD	Median	25–75 pc	Cases, <i>n</i>	<i>p</i> value
Tree early pollen (tree I)	10.1 $\pm$ 5.10	10	5–15	204	<0.0001*
Tree late pollen (tree II)	10.1 $\pm$ 4.99	10	5–15	214	<0.0001*
Grass	10.3 $\pm$ 5.18	10	5–15	194	<0.0001*
Weeds	10.5 $\pm$ 5.32	10	5–15	121	<0.0001*
House dust mites	10.5 $\pm$ 5.65	10	5–15	278	<0.0001*
Fungi	10.5 $\pm$ 5.91	10	5–15	101	<0.0001*
Pets (dog and cat dander)	10.4 $\pm$ 5.53	10	5–15	283	<0.0001*
Control group	7.25 $\pm$ 4.3	5	5–10	96	

* *p* – probability value versus control group (Mann-Whitney U test). Values in bold indicate significant differences.

Eosinophilia in nasal smears in patients was significantly ($p < 0.0001$) higher in groups of intermittent and persistent moderate/severe AR compared to intermittent and persistent mild AR.

Results for groups:

Intermittent mild – median: 3, 25–75%: 2–4, mean 2.95 ± 1.0 , persistent mild – median: 3, 25–75%: 2–4, mean 2.97 ± 1.1 , intermittent moderate/severe – median: 4, 25–75%: 3–5, mean 4.15 ± 1.9 , persistent moderate/severe – median: 4, 25–75%: 3–5, mean 3.87 ± 1.8 (Fig. 3).

All AR patients had nasal eosinophilia significantly ($p < 0.0001$) higher compared to controls (mean 3.40 ± 1.5 , median: 3, 25–75%: 2–4, and mean 0.07 ± 0.3).

A weak, but significant positive correlation was observed between the nasal MCT and the percentage of eosinophil cells in nasal smears ($r > 0.10$, $p < 0.008$). This positive relationship supports the idea that nasal allergy, expressed as a rising percentage of eosinophils in nasal smears, adversely affects the MCT.

No correlation was observed between the MCT and: participant age, total serum IgE concentration, vitamin

Table 2. Spearman's correlations between MCT and other parameters in the group of children with AR

Correlation	<i>r</i>	<i>p</i> value
Nasal eosinophilia: MCT	0.10	<0.008
Vitamin D3 concentration: MCT	−0.03	<0.606
Total IgE concentration: MCT	0.05	<0.206
Blood eosinophilia (percentage): MCT	0.02	<0.671
Blood eosinophilia (absolute number): MCT	0.03	<0.427
Age: MCT	0.03	<0.399
Duration of the illness: MCT	0.07	<0.202

r, correlation ratio; *p*, probability value; MCT, mucociliary clearance time; AR, allergic rhinitis. Value in bold indicate significant difference.

D3 serum concentration, the absolute number or percentage of eosinophils in blood, duration of illness. The skin wheal sizes after prick tests with the common allergens also did not correlate with MCT.

The results are shown in Table 2.

Significant positive correlations were noted between MCT and some specific serum IgE concentrations in AR patients: Hazel (*Corylus avellana*), Alder (*Alnus glutinosa*), Birch (*Betula alba*), *Cladosporium*, and dog dander (*Canis familiaris*). The results are given in Table 3.

Discussion

Our results confirm that AR affects mucociliary clearance in children. Our findings, based on the test results obtained from over 800 children suffering from AR, indicated significantly longer MCT than in peers without AR. Dividing the AR patients into the 4 ARIA classes we noted significant differences in the MCT between the most severe and the mild classes of AR [17]. Our observations of the more impaired mucociliary clearance in the intermittent and persistent moderate/severe AR support the idea of the harmful effect of the local inflammation on cilia functioning. These findings contradict those of Corbo et al. [13] who did not observe any significant differences in MCT between healthy subjects and AR patients. Although many potential mechanisms have been suggested [20, 21], the exact cause of the disturbed function of cilia in rhinitis allergy remains unclear. The major effect of inflammatory mediators on mucociliary function may be associated with the IL-13 induced mucociliary beating impairment [22] and with leukotriene D4, which stimulates the ciliary activity simultaneously impairing the cilia in orientation [23].

As in the present study, previous reports noted additional worsening of the mucociliary function due to the clinical severity [10]. We also noted significantly higher values of MCT in patients with intermittent and persistent moderate/severe AR class compared to both mild AR and controls. Our findings indicate that worsening of the AR symptoms, reflected in the higher nasal eosinophilia [24], positively correlated with clearance time but not with the eosinophilia level in blood or total IgE concentration. This relationship between MCT and nasal eosinophilia suggests that locally induced immune reactions are associated with nasal cilia dysfunction; the same positive correlation was also confirmed in non-AR patients [21]. These findings indicate that eosinophils and their products play a detrimental role in the functioning of nasal cilia in AR patients.

In the present study, no relationship was observed between age and clearance time in the AR children, nor between disease duration and MCT, suggesting that MCT does not decrease over the course of AR or during adolescence. This is promising news regarding the potential of AR treatment to reverse dysfunctions in mucociliary clearance. Many clinical trials have confirmed that ciliary dysfunction is not a permanent pathology: Significant improvement of MCT was noted after nasal topical steroid treatment [15] and allergen immunotherapy [16].

A significant positive correlation has been observed between MCT and the magnitude of the skin prick allergen reactivity to some common allergens [12]. However, no such relationship was found in the present study, even though MCT correlated positively with the serum concentration of specific IgEs to common allergens, but not to other allergens. Unfortunately, further studies are needed to determine the mechanism behind this phenomenon. In addition, no correlations were found between total IgE serum concentration, blood eosinophilia, and MCT.

A low level of vitamin D3 was found in the majority of children suffering from primary ciliary dyskinesia. It is well known that vitamin D3 influences the function of immune cells and resistance to respiratory tract infections [25]. Its other important activities concern the stimulation of Treg cell proliferation down-regulating the likelihood of allergic reactions, moreover the vitamin improves the integrity of the airway epithelial barrier [26, 27]. Many studies report that adequate vitamin D concentration improves the course of AR [28]; however, no such correlation was found between vitamin D level and MCT in the present study indicating that mucociliary clearance does not depend on vitamin D level.

Table 3. Spearman's correlations between MCT and specific serum IgE concentrations in the group of children with AR

Correlation	N	r	p value
sIgE against <i>Corylus avellana</i> : MCT	179	0.19	< 0.026
sIgE against <i>Alnus glutinosa</i> : MCT	176	0.22	< 0.003
sIgE against <i>Betula alba</i> : MCT	147	0.19	< 0.028
sIgE against <i>Quercus robur</i> : MCT	89	-0.07	<0.517
sIgE against <i>Phleum pratense</i> : MCT	137	-0.09	<0.288
sIgE against <i>Plantago lanceolata</i> : MCT	66	0.06	<0.664
sIgE against <i>Artemisia vulgaris</i> : MCT	88	0.05	<0.684
sIgE against <i>Dermatophagoides farinae/D. pteronyssinus</i> : MCT	238	0.11	<0.092
sIgE against <i>Penicillium notatum</i> : MCT	30	0.09	<0.645
sIgE against <i>Alternaria tuis</i> : MCT	46	-0.04	<0.810
sIgE against <i>Cladosporium herbarum</i> : MCT	41	0.33	< 0.042
sIgE against <i>Aspergillus fumigatus</i> : MCT	33	-0.01	<0.947
sIgE against <i>Canis familiaris</i> : MCT	211	0.16	< 0.025
sIgE against <i>Felis domesticus</i> : MCT	217	0.03	<0.634

N, number of cases; r, correlation ratio; p, probability value; MCT, mucociliary clearance time; AR, allergic rhinitis. Values in bold indicate significant differences.

Conclusion

AR affects mucociliary clearance in children, and its deterioration is related to the severity of the disease and the intensity of local nasal inflammation, reflected in nasal smear eosinophilia. MCT correlated with blood concentration of IgE to only chosen common allergens. Our findings indicate that the results of the skin prick test, vitamin D serum level, total blood IgE concentration, blood eosinophilia, patient age, and disease duration do not have any marked relationship with nasal MCT.

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None.

Statement of Ethics

The study was approved by the Bioethics committee of the Medical University of Lodz (nr RNN/216/15/KE).

Written informed consent were obtained from the participating subjects themselves and their parents or legal guardian.

Disclosure Statement

The authors have declared that they have no conflict of interest in relation to this work.

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Author Contributions

M.M. was responsible for data acquisition, main writing of the manuscript, figure design, and critically revising the manuscript for important intellectual content. K.J. was responsible for data acquisition, writing of the manuscript, figure design, and critically revising the manuscript for important intellectual content. Z.B. was responsible for writing of the manuscript, figure design, and critically revising the manuscript for important intellectual content. E.M. was responsible for writing of the manuscript, figure design, and critically revising the manuscript for important intellectual content.

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