IMPAIRED RESPIRATORY FUNCTIONS IN CHILDREN WITH CAT SENSITIZATION IN THE EARLY AGES OF CHILDHOOD

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Abstract

Objective: To evaluate respiratory functions in children with cat sensitization using impulse oscillometry (IOS) and spirometry and to compare these with those of healthy controls. **Methods:** This prospective case-control study included 130 children aged 3-17 years with cat sensitization (CS group) accompanying respiratory allergic diseases (Group I: asthma, Group II: allergic rhinitis, and Group III: co-existent asthma and allergic rhinitis), and 70 age- and sex-matched healthy controls (HC group). The cases' demographic parameters were recorded, and respiratory functions were analyzed using IOS and spirometry. The association between IOS and spirometric parameters was also evaluated. **Results:** At IOS evaluation, zR5, R5-20, Fres, and AX values were higher in children in the CS group compared to the HC group (p=0.029, p=0.008, p=0.001, and p<0.001, respectively), while zX5 and zX20 values were lower (p=0.001 and p<0.001). R5-20 and AX were higher in asthma compared to allergic rhinitis (p=0.008, 0=0.015), but were insignificant compared to both together. R5-20, Fres, and AX were higher, and zX20 was lower in the pre-school age group (p<0.001). No correlation was found between zFEV1, zFVC, zFEV1/FVC, zFEF25-75 and zR5 values in the CS group (p>0.05). **Conclusions:** Pulmonary resistance was higher and reactance was lower in the entire and peripheral airways in children with cat sensitization accompanying respiratory allergic diseases compared to the healthy controls. Peripheral airway resistance and reactance were more impared in asthma group compared to allergic rhinitis. However, peripheral airway resistance and main airway reactance were more impaired in the pre-school age group than in the older age group.

INTRODUCTION

The domestic cats (Felis catus) have long been known to be one of the most common respiratory allergens.[1] Cat sensitivity rates vary between 20% and 50% in previous studies.[2,3] Cat allergen is the second most frequent indoor allergen and the third most common among all aeroallergens after pollens and house dust mites.[4] More than 350,000 emergency room visits occur due to cat allergy-related asthma attacks in the USA every year.[5]

Cat sensitization seems to be one of the most important risk factors for both the development of asthma and the rising frequency of asthma attacks.[5,6,7] However, there are also some contradictory findings in the literature suggesting that cat sensitization may increase respiratory symptoms a non-linear manner with exposure or that intense exposure to cats at early ages may be even protective.[8-12] Recent studies have shown that asthma severity, the frequency of wheezy attacks, medication requirements, and unpredictable physician visits due to allergic respiratory symptoms resulting from cat allergen exposure increase with cat sensitivity in children.[13-16]

Although conventional spirometry is a highly valuable test for detecting airway obstruction and diagnosing asthma, it is also subject to a number of limitations. Being effort-dependent and requiring high cooperation,

it is difficult for children, particularly those of preschool-age. In addition, it does not provide sufficient information about peripheral airways.[17] Impulse oscillometry (IOS) is a standardized, non-invasive, practical alternative test that requires less effort than spirometry. It is very useful for measuring entire and peripheral respiratory functions, particularly in preschool-age children unable to adapt to spirometry. IOS also provides important data regarding the deterioration in airway function that may develop in children with respiratory allergic diseases at early ages, and also yields more specific data about lung resistance, reactance, and peripheral airway obstruction.[18,19]

This study was set out to evaluate the respiratory function tests of children with cat sensitization and respiratory allergic diseases (asthma and/or allergic rhinitis) using IOS and spirometry, respectively, and to compare the resulting data with those of healthy controls, and also to evaluate the potential risk factors that may affect lung functions.

METHODS

Study Population

This prospective case-control study was conducted with 130 children aged 3-17 years with respiratory allergic diseases including asthma, allergic rhinitis, both together, and cat sensitization (CS group), between January 2022 and November 2023 in a tertiary referral center.

All children with cat sensitization while under follow-up by the pediatric allergy department with diagnoses of asthma and/or allergic rhinitis and whose diseases had been under control for at least three months of treatment were enrolled in the study. Age- and sex-matched healthy controls (HC group, n=70) who had presented for routine health checks were accordingly recruited from the general pediatric outpatient clinic.

CS group was divided into three groups according to their diagnoses. The first group consisted of patients with asthma (Group I, n=26), the second of patients with allergic rhinitis (Group II, n=47), and the third of patients with co-existent asthma and allergic rhinitis (Group III, n=57). They were also divided into two subgroups according to domestic cat exposure (Group Do+, n=12) or non-exposure (Group Do-, n=118). They were further subdivided into two groups on the basis of age, the first consisting of pre-school age children (3-6 years, n=25), and the second of school-age children and adolescents (7-17 years, n=105). Additionally, were finally assigned into two groups based on treatment steps for asthma, the first consisting of children under step 2 treatment (n=34) and the second of those under step 3-4 treatment (n=49).

Definitions

Asthma is defined as a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitation. Patients with characteristic asthma symptoms were diagnosed by means of spirometry and reversibility testing in accordance with the Global Initiative for Asthma (GINA) guideline. Patients younger than five were diagnosed on the basis of symptoms and inhaled corticosteroid responsiveness. All the patients had been under control with step 2-4 treatment for at least three months.[20]

Allergic rhinitis was defined as symptoms of nasal itching, congestion, rhinorrhea, and sneezing according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. The condition was classified as intermittent or persistent depending on duration and as mild or moderate to severe according to severity.[21]

Skin prick test

Skin prick tests were performed using a prick test applicator (MedBlue One) on the flexural aspect of the forearm in line with standard guidelines, using standardized glycerinated extracts from LOFARMA (Milan, Italy) (1% weight/volume). Cat sensitization was defined as positive in children with a skin prick test induration diameter [?]3mm for cat epithelium solution.[22] Detailed information about skin prick testing was given in supplementary data.

Exclusion criteria

The exclusion criteria for the study group were a history of chronic lung disease (except for asthma), first- and secondhand smoking exposure, chronic cardiac and neuromuscular disease, a history of low birth weight/premature birth/neonatal mechanical ventilation, malnutrition, obesity, malignancy, immune deficiencies, connective tissue disease, acute or chronic respiratory disease (adenoid hypertrophy or chronic sinusitis etc.) in the previous four weeks, or history of hospitalization or admission to intensive care unit in the previous year. Patients using inhaled short-acting beta agonists, systemic steroids, anticholinergics, and decongestants were also excluded from the study.

Exclusion criteria for the HC group were the presence of allergic respiratory diseases such as asthma and allergic rhinitis in addition to the criteria listed above.

Study design

When patients with asthma and/or allergic rhinitis presented to the pediatric allergy outpatient clinic for skin prick testing, those with cat sensitization were invited to take part in the study. Routine physical examinations were performed, and anthropometric measurements were recorded on the patients who agreed to participate in the study. Routine endoscopic authorhinolaryngological examinations were performed in the Ear-nose-throat (ENT) clinic in order to exclude any allergic rhinitis complications and/or comorbidities such adenoid hypertrophy or acute/chronic sinusitis. The patients were then referred to the respiratory function tests laboratory for IOS and spirometry.

Age- and sex-matched healthy subjects who had presented for routine health checks were randomly recruited from the general pediatric outpatient clinic and invited to participate in the study. Routine physical examinations were conducted, anthropometric measurements were recorded, and these were then referred to the respiratory function test laboratory.

Pulmonary Function Tests

All patients were referred to the respiratory function test laboratory one hour after skin prick testing. Respiratory function testing commenced once the participants had been sitting calmly for at least five minutes. IOS was first applied to all the patients and healthy controls. Spirometry was performed after oscillometric measurements on all participants older than five years.

Impulse Oscillometry

A Jaeger MasterScreen IOS system (Jäeger, Wurzburg, Germany) was used to measure the input impedance of the respiratory system. This was performed in line with American Thoracic Society/ European Respiratory Society guidelines.[23] The IOS technique is used to measure pulmonary resistance (R) and reactance (X). The flow signals were evaluated for 30s in a frequency range of 5 to 20Hz for amplitude differences to determine R and X values. The main parameters of IOS include resistances [R5, R20 R5-20 (resistance at 5 Hz minus resistance at 20Hz)] and reactance [X5, X20, resonant frequency (Fres) and reactance area (AX)].[18] Higher frequencies of R (˜20Hz), reflecting the larger airways, were regarded as representing resistance in central airways. Lower frequencies of R (˜5Hz) provided information about the totality of airways (both small and large). Peripheral (small) airway resistance was defined as R5-20. Acceptable variability was 15%. The coherence thresholds were set to [?]0.6 at 5Hz and [?]0.8 at 20Hz.[24,25] R5, R20, X5, and X20 were transformed into z-scores from reference data to adjust the values for age and gender. R5-20, Fres, and AX were used as measured crude values because of the lack of references.[26]

Spirometry

The spirometry test was performed using a Jaeger MasterScreen IOS system (Erich Jaeger, Hochberg, Germany). The precise technique employed for this study was based on the recommendation in the American Thoracic Society official statement on the standardization of spirometry.[27] The acceptable coefficient of variation was <10%. Lung function parameters were expressed as percentage values (%) predicted using Hankinson's formula.[28] Z-scores for spirometric parameters (zFVC, zFEV1, zFEV1/FVC, zFEF25-75) were elicited using Global Lung Initiative equations.[29]

Ethics

The study was approved by our institution's local research ethics committee (2022/121). All participants took part voluntarily, and written informed consent was obtained from the parents of all children and also personally from children older than 12.

Sample Size

For statistical power analysis, due to the lack of previous studies evaluating lung functions with IOS in children with cat sensitization and respiratory allergic diseases; sample size was measured according to the effect size (Cohen's d) as 0.5. Analysis using G*Power 3.1.9.7 revealed that at an effect rate of 0.71, a margin of error of 0.05, and a critical t value of 1.65 at an effect power of 85%, least 59 patients would be required in each group. In the light of potential losses of 10% that might occur during the lung function measurements, we planned to include at least 65 patients in both groups, yielding a total of 130 participants.

Statistical Analysis

SPSS version21.0 statistical software (SPSS for Windows 21.0, IBM SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Categorical variables are presented as numbers (%) and continuous variables as mean+-SD and median values (interquartile range-IQR). Univariate analyses involving categorical data were performed using thex^2 test. Data from pulmonary function tests exhibiting parametric variables according to the Shapiro-Wilk normality test, were analyzed using Student's t-test, and nonparametric variables using the Mann-Whitney U test (comparison between the patient and healthy groups and Groups Do+ and Do-). Kruskal-Wallis test was applied to compare differences among groups asthma, allergic rhinitis and coexistent of both as they were nonparametric data. Spearman's correlation analysis was applied to non-parametric continuous variables. A value of $p<0.05$ were considered statistically significant.

RESULTS

Cat sensitization was detected by skin prick testing in 182 children with asthma and/or allergic rhinitis. All these patients had been under medical treatment and follow-up in our pediatric allergy and immunology clinic for at least three months, and all were requested to participate in the study. However, 11 declined and 41 were excluded due to meeting the exclusion criteria. Ninety-six age and sex-matched children were randomly selected for the healthy control group. However, seven declined to participate, three were unable to cooperate with the pulmonary function tests, and 16 were excluded due to passive smoking exposure. The study flowchart is shown in Figure 1.

A comparison of demographic and clinical data between the children with respiratory allergic diseases and the HC group is presented in Table 1. No differences were determined between the groups in terms of the demographic characteristics of sex or age, or weight, height, and BMI z scores ($p>0.05$).

The median enduration size was 5.5 mm (range 4.5mm to 6.12 mm) at skin prick testing with a standardized cat allergen solution. Only 9.23% (n=12) of the CS group experienced domestic cat exposure in the home. When atopy status was evaluated, 91.53% (n=119) of those were polysensitized, and pollen allergy was the most frequent allergen accompanying cat sensitization. Eosinophilia was detected in 36.92% (n=48) of the patients.

At IOS analysis, zR5, R5-20, Fres, and AX levels were higher and zX5 and zX20 lower in children with respiratory allergic disease compared to the healthy controls ($p=0.029$, $p=0.008$, $p=0.001$, $p<0.001$, $p=0.001$, and $p<0.001$, respectively). A comparison of IOS parameters between the children with respiratory allergic disease and controls is shown in Table 2 and Figure 2.

A comparison of the IOS and spirometry values of groups I, II, and III is shown in Table 3. No differences were determined between those groups in terms of the demographic characteristics of sex and age, weight, height and BMI z-scores ($p>0.05$). Analysis of the IOS and spirometry parameters revealed no significant difference was found among the three groups ($p>0.05$).

A comparison of IOS parameters according to cat exposure is shown in Table 4. No difference was observed in terms of IOS parameters or spirometric values between the Do+ and Do- groups ($p>0.005$).

A comparison of IOS parameters according to age groups is given in Table 5. In terms of airway resistance, R5-20 was higher in preschool age compared to the older age group ($p<0.001$). In terms of airway reactance, zX20 was lower, Fres and AX were higher in the pre-school age group, than in the older age group ($p<0.001$).

No difference in terms of IOS parameters was observed between the step 2 and step 3-4 treatment groups ($p>0.05$). No correlation was found between zFEV1, zFVC, zFEV1/FVC, zFEF25-75, and any IOS parameter in the CS group ($p>0.05$). Similarly, no strong correlation was detected between IOS and spirometry values, according to gender, treatment step of asthma, allergic respiratory disease subgroups, and cat exposure. However a moderate positive correlation between zFEV1 and zR20 in girls ($r=0.428$, $p=0.016$), and a moderate negative correlation between zFEV1/FVC and AX in asthma patients ($r=-653$, $p=0.11$) were detected.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the respiratory functions of children with cat sensitization and respiratory allergic diseases (asthma and/or allergic rhinitis) using the IOS and also spirometry. The results revealed an increase in airway resistance and a decrease in reactance parameters of the entire and peripheral airways measured using IOS, while no difference was determined using spirometry, in CS group compared to the HC's. Peripheral airway resistance and reactance were more impaired in asthma group compared to allergic rhinitis, but it was insignificant to coexistent asthma and allergic rhinitis. Our findings are particularly valuable since they show that respiratory functions are unrelated to domestic cat contact in the home and peripheral airway resistance and main airway reactance were worse in pre-school age patients than in older children. No difference was observed between the Step 2 and Step 3-4 treatment asthma groups in terms of IOS or spirometry parameters. The study results are important because they show that cat allergy begins in the entire and/or peripheral airways in early childhood, even if respiratory function tests with spirometry are normal, in the absence of cat contact at home and in various asthma severity.

In terms of resistance, higher zR5 showed an increase in entire airway resistance, while the higher R5-20 parameter revealed an increase in peripheral airway resistance. In terms of reactance, the decreases in zX5 and zX20 indicate reactance impairment in the total airway and the increase in Fres and AX in the peripheral airway.[24] We claim that early stages of lung function deterioration could not be detected by traditional spirometry, and it may be unable to reveal the respiratory functions of peripheral airways. In contrast, an earlier cohort study performed respiratory function tests using IOS and evaluated specific IgE for aeroallergens in 486 randomly selected children aged 11 years, and found that these parameters were not significantly affected in participants with cat sensitization.[30] In this population based study, the low number of participants with cat sensitivity and asthma, the high number of patients who could not undergo IOS, and the fact that IOS parameters were given as crude values may have affected the results.

Cat allergen sensitivity varies depending on the individual's atopy status, environment and the duration of exposure.[10]Interestingly, only 10% of the children with cat sensitization in this study were exposed to cats in their homes. Although the rate of exposure to domestic cats was low, we may nevertheless speculate that cat allergen concentrations may have risen in recent years due to global warming, their being easily spread, small in size, and more suspended in the air, and since they spread more easily in social environments, especially in closed areas such as schools.[31] It is well known that cat allergen is frequently detected in house dust in shopping malls, classrooms, and examination rooms, being carried on people's clothing and hair, even if there are no cats in the immediate environment.[32] Probably due to this reason, we could not detect any difference between the respiratory function tests of groups Do+ and group Do-. In Simoneti's cohort, the frequency of asthma increased among individuals with cats at home, although their spirometry values were not different from those of the other groups (who kept dogs at home or who never had pets).[15] In Leung's study, the presence of cat allergen in the home significantly increased the level of Feld1 in house

dust, although no correlation was observed between the household cat allergen level and FeNO or spirometry values.[14] In Langley's study from 2003, high exposure among sensitive patients to cat allergen in the home was associated with decrease in FEV1, and increase in FeNO, and more severe bronchial hyperreactivity.[33] Zeidler et al. studied the respiratory function tests of cat-allergic asthmatic patients with natural cat exposure. No significant change was observed in FEV1 during tests performed before and at the 6th and 23rd hours after exposure, while a significant decrease in FEF25-75 and FVC was observed at the 6th hour. Moreover, increased air trapping at HRCT and bronchial hyper-reactivity were observed at the 6th and 23rd hours after cat exposure. Small airway obstruction and bronchial hyper-reactivity may therefore have persisted until the 23rd hour with natural cat exposure.[34]

Surprisingly, we observed no difference between the Step 2 and Step 3-4 treatment asthma groups in terms of IOS or spirometry parameters as all participants were under regular medication and disease control for at least three months. However, Konradsen et al.'s study showed that cat and dog allergies were associated with more severe childhood asthma.[11] Another study comparing the clinical and laboratory characteristics of patients with cat allergy and asthma in terms of domestic cat exposure reported no difference in respiratory function tests, nasal-ocular symptoms, or asthma control tests, although the group with domestic cat exposure required higher potency steroids and longer-acting beta agonists. The authors also showed that living with a cat in the home despite allergies necessitated the use of more preventive medications.[16]

The principal strengths of this study include the fact that allergic rhinitis and asthma were diagnosed by pediatric allergy specialists working in a tertiary referral center, all lung function measurements being performed by the same physician and nurse to the same standards. IOS and spirometry, respectively, were performed to eliminate conflicting test results. All children were evaluated by ENT physicians before recruitment in order to exclude diseases that might affect pulmonary functions. Particular care was taken to ensure that all patients' asthma was under control, that they had no active infection, and that they received Step 2-4 ICS therapy at least three months. Additionally, patients with pollen allergy were included in the study during a period outside the pollen season.

The principal limitation of this study is that the results cannot be generalized to the entire population due to its single-center and cross-sectional nature. Another limitation involves the lack of mono-sensitized cat-allergic children. More than 90% of the patients with cat sensitization in this population had poly-sensitization. However, based on our current data, it was not possible to predict the effects of poly-sensitization in most of our patients or the effects of other allergens on respiratory function tests. As there is no z score of Fres and a higher expected crude value for young children, might impact our results. Another limitation of the study was the presence of participants who could not perform spirometry, particularly those under five years of age due to their inability to comply with the test. Moreover, cross-sectional evaluation of the children during a single time period measurement limited our data concerning the change in lung functions according to cat allergen exposure or treatment response. We were also unable to measure indoor Feld1 concentrations in the patients' homes for the purpose of investigating the causal association between deterioration of lung functions and exposure to allergen concentrations.

CONCLUSION

This study shows, for the first time in the literature, that children with respiratory allergic diseases and cat sensitization exhibited increased entire and peripheral airway resistance and decreased reactance compared to age- and sex-matched healthy controls. Domestic cat exposure was not related to increased respiratory function deterioration, and may therefore be more associated with cat allergens being small in size and with their ability to spread easily in social areas. In addition, the present study will contribute significantly to the existing literature as the first to show commencement of early airway obstruction at early ages in children with cat sensitization irrespective of spirometric lung function tests being normal, the presence or absence of exposure to domestic cats in the home, the condition being under control with regular medication, and asthma severity. We suggest that further, multi-center cohort studies with larger populations are now needed to strengthen our preliminary results. Further research is now required in order to elucidate the molecular and clinical aspects of cat allergy in childhood, and to identify its effect on respiratory functions, as we are

clearly still looking at the mere tip of a whole iceberg of unknown factors.

Conflicts of interest

There are no conflict of interest declared.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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