Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "Allergy Newsletter" which contains latest and interesting news in the field of Allergy.

This issue contains:

1. **Evaluation of comorbidities associated with chronic rhinosinusitis in children and adults**
2. **Assessment of specific bronchial symptoms in asthma diagnosis and their control in patients with rhinitis**
3. **Evaluation of efficacy and safety of intratonsillar immunotherapy in allergic rhinitis**
4. **Case report on Birt-Hogg-Dube syndrome**

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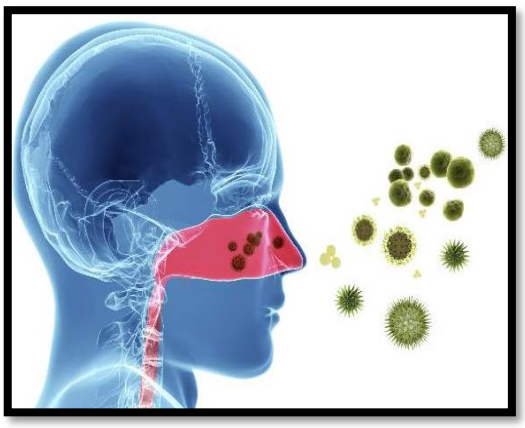
Looking forward to your valuable feedback
Best Regards,
Medical Team, Micro Labs Ltd

Evaluation of comorbidities associated with chronic rhinosinusitis in children and adults

Introduction



Chronic rhinosinusitis (CRS) is a persistent inflammatory condition affecting the nasal and paranasal mucosa lasting more than 12 weeks which can led to significant health burden. CRS is classified into two sub-forms based on appearance of the nasal cavities on endoscopy, i.e., with nasal polyps (CRSwNP) and without (CRSsNP). In Europe, the estimated prevalence of CRS is 11%, while that of CRSwNP is 1-4%. Pediatric CRS (PCRS) affects around 2.1– 4% of the population.[1] CRS is commonly associated with other atopic conditions, such as asthma and allergic rhinitis, necessitating an integrated treatment approach.[2] This study aims to evaluate relative proportion of different phenotypes, comorbidities, Endoscopic sinus surgery (ESS), and risk factors associated with revision surgery in pediatric and adult population.

Methods

This retrospective registry-based study was carried out based on the hospital registry data. Random sample of rhinosinusitis patients (age range 0–89 years) with the diagnosis of J32 or J33 were included. Collected covariates included personal characteristics (gender, age), disease of interest (CRS), phenotypes of interest (CRSwNP, CRSsNP), and coexisting diseases. ESS operations of the nose and maxillary antrum, as well as surgery of the ethmoidal, frontal and sphenoidal sinuses, were also included. Statistical methods were used to identify significant associations and patterns between CRS and various comorbid conditions.

Results

The study examined the comorbidities associated with chronic rhinosinusitis (CRS) in both pediatric and adult populations, revealing significant findings. Among 1,357 pediatric patients, common comorbidities included allergies (57%) and asthma (47%), with notable incidences of tonsil disease (21%) and chronic otitis media (COM) (19%), other chronic pulmonary diseases in 14%, eosinophilia in 10%, diabetes in 10%, and immunodeficiency or its suspicion in 4.0% of cases as comorbidity. In contrast, the 1,357 adult patients had a lower prevalence of these conditions, with asthma (38%) and allergies (34%) being the most common comorbidities. Other chronic pulmonary diseases existed in 23%, eosinophilia in 17%, diabetes in 11%, tonsils disease in 4.9%, immunodeficiency or its suspicion in 3.6%, and chronic otitis media in 2.4% of cases as comorbidity in adults (Figure 1). The study also highlighted significant differences between children and adults: allergies, chronic otitis media, and tonsil disease were more prevalent in children. Additionally, baseline ESS was performed on 41% of children and 46% of adults, with

adults requiring more revision surgeries, particularly those with conditions such as asthma, CRSwNP, and NERD.

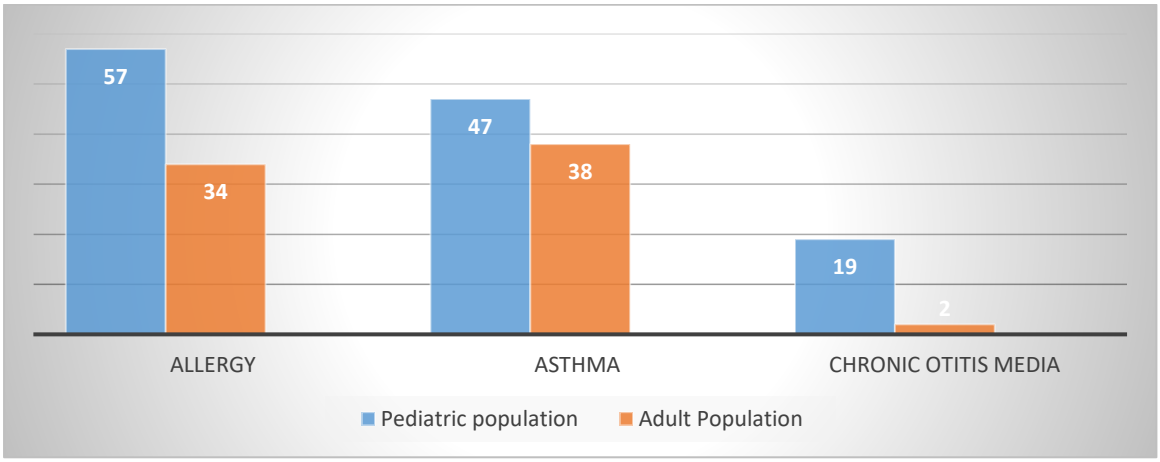


Figure 1. Comorbidities in children's and adults

Discussion

This study finding showed that allergy (53.2%) and asthma (41.3%) were the two most frequent comorbidities among PCRS patients.[1] These results were similar with the Anamika A et al. study that reported 53% of PCRS patients tested positive on skin prick tests.[3] Among adults Allergy, asthma, and other chronic respiratory diseases were highly prevalent with CRS. It was found that in all pediatric patient's relative proportion of NERD was 3.97% and 20% among pediatric CRSwNP patients. In the adult group, the relative proportion of NERD was 8.05% among all patients and 16.7% among patients with CRSwNP. Eosinophilia was found to be most prevalent in adults with CRSwNP. Comorbidities that significantly differed between pediatric and adult patients were allergy, COM, and tonsils disease. In both age groups high overlap of allergy and asthma with CRS, but the overlap was more pronounced in children. Risk of revision ESS was increased in the presence of allergy, asthma, NERD, eosinophilia, immunodeficiency or its suspicion, having two or more comorbid diseases, and nasal polyps.[1]

Conclusion

Allergy, Asthma, chronic otitis media, mental health disorders, and tonsils disease were significantly more prevalent among pediatric patients. ESS was equally prevalent in children and adults with CRS.

Allergy and Asthma were the most common comorbidities in both pediatric and adult population.

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Assessment of specific bronchial symptoms in asthma diagnosis and their control in patients with rhinitis

Introduction

Wheezing and chest tightness were the symptoms of asthma having highest specificity for asthma diagnosis

Asthma is a defined as a chronic inflammatory disease of the airways which leads to cough, wheeze, shortness of breath, and chest tightness. Symptoms of asthma are caused by the inflammation of the airways, which triggers processes such as mucus production, remodeling of the airway wall, and bronchial hyperresponsiveness (BHR).[1] Many patients with asthma are insufficiently monitored and exhibit poor adherence to treatment. These factors contribute to poor asthma control, increased risk of asthma attacks, and higher healthcare utilization. Patient-centered digital solutions, including mHealth apps, can potentially address some of these issues by collecting real-world data on asthma symptoms and treatment. The MASK-air (Mobile Airways Sentinel networK) app, which includes validated patient-reported outcome measures (PROMs) like the Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaire, is one such solution.[2] This study aimed to assess how individual asthma symptoms (wheezing, dyspnea, chest tightness) are associated with both asthma diagnosis and control using MASK-air PROMs data.

Methods

This cross-sectional study utilized MASK-air data to compare the frequency of five asthma symptoms (dyspnea, wheezing, chest tightness, fatigue, and night symptoms) in patients with probable asthma, possible asthma, and no evidence of asthma as assessed by CARAT. This study included patients who were diagnosed with asthma. The MASK-air app includes daily monitoring questionnaires and the CARAT questionnaire, assessing the impact of asthma and rhinitis symptoms, and the daily use of medication.

Results

This study included 951 patients with rhinitis, with 468 classified as having probable asthma, 166 with possible asthma, and 317 with no evidence of asthma. There were 2154 CARAT assessments, with 302 indicating controlled CARAT and 1852 indicating uncontrolled complete CARAT. When comparing patients with “no evidence of asthma” versus those with “probable or possible asthma”, wheezing had the highest specificity (90.5%) and positive predictive value (PPV) (90.8%) for asthma diagnosis. Dyspnea had the highest sensitivity (63%). Similar patterns were observed when all CARAT assessments were considered. When comparing patients with “probable asthma” versus those with “possible asthma” specificity decreased from chest tightness (79.5%) and wheezing (77.7%) to dyspnea (64.5%) and fatigue and night symptoms (50%). Dyspnea had the highest sensitivity (76.1%). The PPV ranged from 77.9% to 88.9%. In the Twinning project sample (283 participants), wheezing again showed the highest specificity (86.0%) and PPV (70.5%), while dyspnea had the highest sensitivity (76.3%) and negative predictive value (NPV) (85.6%) (Figure 1). Dyspnea was most strongly

associated with the e-DASTHMA levels, indicating its significance in asthma control assessment.

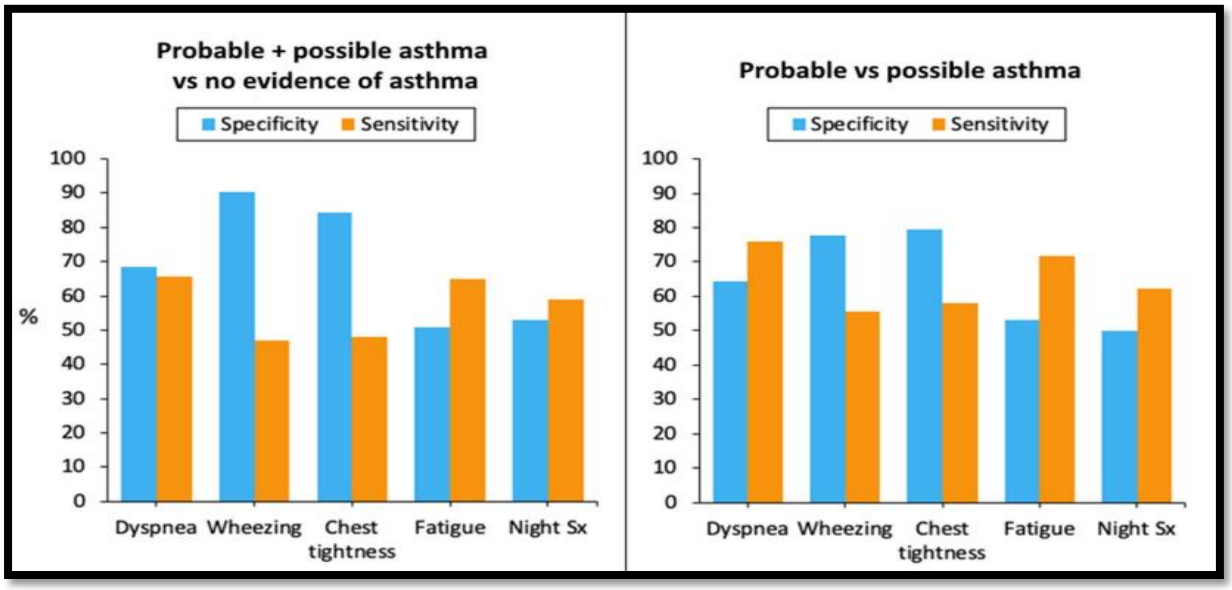

Figure 1. Sensitivity and specificity value in specific asthma symptoms

Discussion

This study was the first to assess individual asthma symptoms for the diagnosis and control of the disease. The study highlights wheezing and chest tightness as significant predictors of asthma diagnosis, with wheezing displaying the highest specificity and PPV.[2] These findings align with previous research indicating wheezing as a crucial symptom for asthma diagnosis.[3] However, dyspnea was the most sensitive symptom for asthma control, corroborating previous studies that found dyspnea to be a key indicator of asthma control and quality of life.

Conclusion

Among patients with rhinitis, wheezing and chest tightness were the most specific symptoms for predicting asthma diagnosis, while dyspnea was the most sensitive symptom for assessing asthma control.

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Evaluation of efficacy and safety of intratonsillar immunotherapy in allergic rhinitis

Introduction

Intratonsillar injection with House dust mite extract was safe and effective in patients with allergic rhinitis

Allergic rhinitis (AR) is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens where it is characterized by sneezing, nasal congestion, nasal itching and rhinorrhoea (nasal discharge).[1] Allergic rhinitis (AR) is a global health issue that significantly affects patients' quality of life. House dust mite (HDM) is a primary allergen causing AR, with approximately 88.9% of AR patients. Allergen-specific immunotherapy (AIT) is the only curative treatment for allergic diseases, inducing tolerance, modifying the disease's natural course, and reducing the risk of further sensitization. Intralymphatic immunotherapy (ILIT) has shown promise for quicker tolerance induction, but it involves complex procedures and potential severe adverse effects. Given the tonsils role in immune tolerance and their accessibility, this study proposes a novel intratonsillar injection immunotherapy (ITIT) route for HDM-induced AR.[2] This study aimed to evaluate efficacy and safety of the intratonsillar injection of house dust mite (HDM) extract in patients with HDM-induced allergic rhinitis (AR).

Methods

This was a investigator-initiated, randomized, double-blind, placebo-controlled trial conducted to evaluate ITIT's efficacy and safety with HDM extract in HDM-induced AR patients. About 80 participants were randomized 1:1 to receive 6 intratonsillar injections of HDM or placebo over three months. Outcomes were assessed at 3, 6, and 12 months post-treatment. Inclusion criteria included aged 18-55 with a history of moderate-to-severe AR, a total nasal symptom score (TNSS) ≥6 and positive HDM sensitivity tests. Primary endpoints were TNSS and change in TNSS (ΔTNSS). Secondary endpoints included visual analogue scale (VAS) scores, combined symptom and medication score (CSMS), and MiniRQLQ.

Results

About 80 patients were enrolled, with 35 in each group completing the study. The TNSS in the active group significantly improved compared with that in the placebo group at 3 months after the treatment was finished. This improvement was not significant at 6 and 12 months, though trends favored the active group. At 3, 6, and 12 months following the end of therapy, the percentage of improved cases in the placebo group was 31.43%, 42.86%, and 37.14%, while the active group had 65.71%, 51.43%, and 57.14% of improved cases at those same intervals (Figure 1). The P values were very close to the significant level, and the number of cases in the active group that improved at more than or equal to two or three visits after the therapy was completed was higher than that of the placebo group (60% and 37.14%, 34.29% and 14.29%).VAS scores, CSMS, and MiniRQLQ showed significant improvements at 3 months in the active group compared to placebo. The Der p-specific IgG4 levels increased significantly

in the active group at all post-treatment assessments ($P < 0.01$). The most frequent AEs were mild local reactions, such as sore throat and throat irritation, which resolved without medical intervention. No severe systemic reactions were observed.

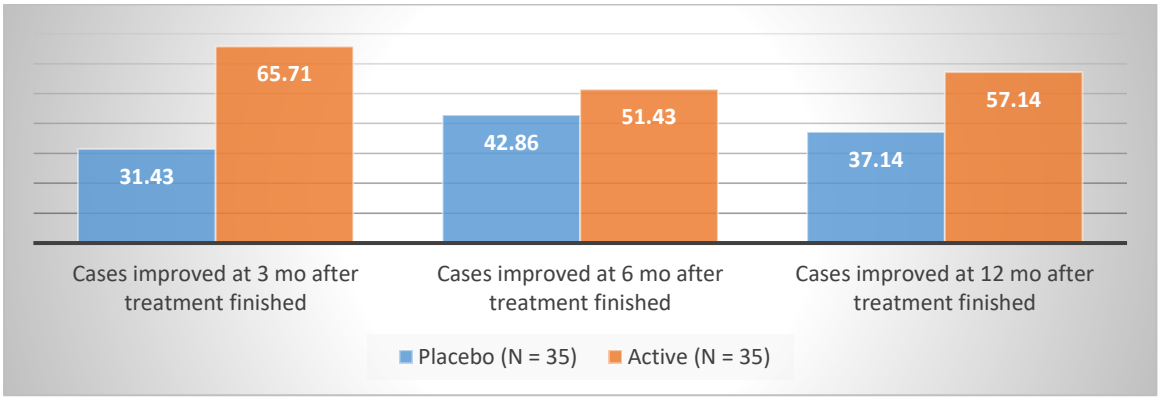

Figure 1. Overall improvement after treatment in per-protocol set

Discussion

In this study, when compared to patients receiving a placebo, the primary end points, TNSS and ΔTNSS, improved significantly (more than 20%) 3 months after patients with AR completed a 3-month, 6 -injection ITIT. At 3, 6, and 12 months following the completion of the treatment, the secondary end points, like the VAS score, CSMS, and quality of life, altered in the same way as the TNSS and ΔTNSS.[2] As previous study has reported that tonsils may serve as powerful inductive sites for immune responses such as immunologic memory and antibody induction.[3] Hence in this study, Intratonsillar allergen injections were found to be safe and tolerated well in this study. HDM intratonsillar injection didn't not cause allergic symptoms such as urticaria and angioedema, which was reported in intralymphatic allergen injections. However, this study was an evidence that intratonsillar injection may be a potential and safe AIT route for AR based on the current results.[2]

Conclusion

Intratonsillar injection with HDM extract was safe and effective in patients with AR. Improving the protocol and allergen formulations is expected to increase and maintain the efficacy of this novel approach.

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Case report on Birt-Hogg-Dube syndrome

Introduction

Birt-Hogg-Dube syndrome is characterized by the development of fibrofolliculomas, lung cysts and subsequent recurrent pneumothorax, and kidney neoplasia.

Birt–Hogg–Dube syndrome (BHDS) is a rare autosomal dominant inherited disorder characterized by pulmonary cysts, spontaneous pneumothorax, skin lesions (fibrofolliculomas and trichodiscomas) and renal tumors. BHDS is caused by germline mutations in the folliculin (*FLCN)* gene, which is present on chromosome 17 (17p11.2).[1] Initial symptoms includes skin lesions which usually appears in the third and fourth decade of life. However, in the later age group fibrofolliculomas can also be present. Diagnosis of BHDS is challenging in the clinical setting. Two major extracutaneous manifestations of BHDS are spontaneous pneumothoraces and renal tumors.[2] This report described the case of 57 years old female with the diagnosis of BHDS.

Case presentation

A 57 years old female patient having a past medical history of osteoarthritis, right vestibular schwannoma status post stereotactic radiotherapy, vulva Bartholin's gland carcinoma, and hypothyroidism presented with the complaints of "hive-like" skin rash in the lower abdominal, pubic, and medial thigh areas that waxed and waned for about 6 months (Figure 1). Fever, myalgia, and fatigue were also present. These symptoms typically occur every 1–3 weeks and resolve after 2–4 days. Based on the signs and symptoms patient was diagnosed as having Urticaria and treated with 5-day course of Steroid. Three weeks later patient's symptoms were worsened and rash developed to face and scalp and upon examination, Chronic Papular Urticaria was diagnosed, and was treated with Cimetidine and topical triamcinolone. Symptoms become more severe and investigation showed elevated levels of CRP (11.8 mg/L). Biopsy was notable for an urticarial tissue reaction with focal changes of leukocytoclasia, while immunofluorescence and serological tests were normal. Later CRP was elevated at 50.4 mg/L. Due this condition patient underwent clinical genomics for full genetic work-up. Upon investigation whole genome sequencing (WGS) showed presence of heterozygous mutation in the FLCN gene with pathogenic variant c.779+1G>T reported to cause autosomal dominant BHDS. Chest Computerized tomography (CT) showed small lung cysts, calcified granulomas and non-calcified pulmonary micronodules (Figure 2). Abdominal Magnetic resonance imaging (MRI) showed 14-mm lesion in the left kidney, likely representing a hemorrhagic or proteinaceous cyst. Patient was advised continued to follow-up with pulmonology, urology, and dermatology on a regular schedule. Patient was advised to minimize activities that can precipitate a spontaneous pneumothorax such as scuba diving, high altitudes and flying. Genetic counselling and testing were performed to family members.

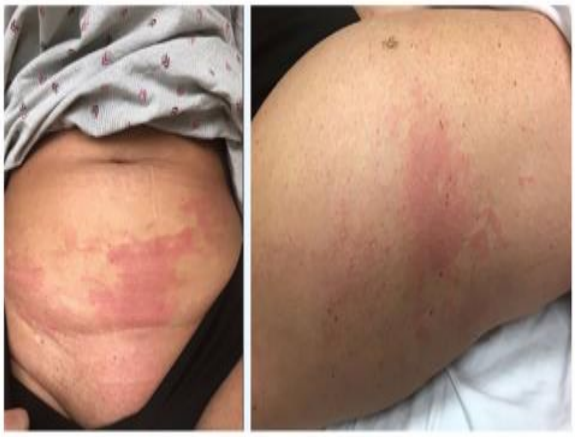

Figure 1. Urticarial-like morphology on lower abdomen/pubic (left) and right lateral thigh region (right).

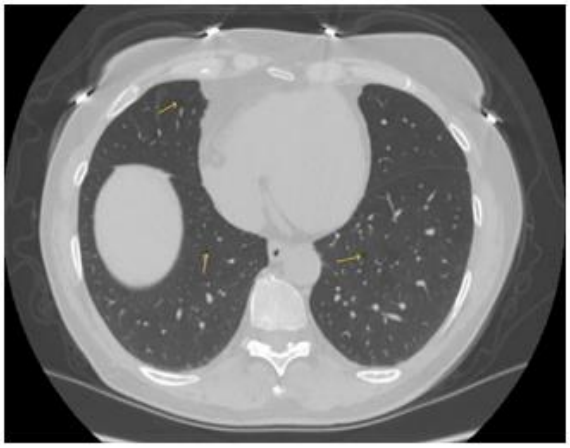

Figure 2. Small areas of cystic lesions scattered across both the lungs (yellow arrow).

Discussion

This study finding suggest that BHDS was known to be caused by germline mutation in the folliculin (FLCN) tumor suppressor gene on Chromosome 17 (17p11.2). In around 85% of BHDS cases, Fibrofolliculomas are the most common cutaneous manifestation. In many cases with individual less than 20 years of age, skin findings might be absent. Pulmonary cystic disease develops in around 70-80% of patients with BHDS which poses many challenges. Pulmonary cystic disease puts the patient at risk of pneumothorax. Adhikari N et al. showed that recurrent spontaneous pneumothorax can often be a presenting symptom for the diagnosis of BHDS.[3] European Birt-Hogg-Dube guidelines for diagnosing BHDS has major criteria which include histologically confirmed fibrofolliculomas/trichodiscomas or Identification of FLCN pathogenic variant and minor criteria includes multiple lung cysts, renal cancer of mixed chromophobe and oncocytic patterns before age 50, and first degree relative with BHDS.[4] Therefore, this case report highlighted the importance of genetic testing in case of BHDS.

Conclusion

Fibrofolliculomas are generally the most common dermatologic manifestation in BHDS and clinicians should be aware of other skin presentation such as urticarial vasculitis.

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