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This issue contains:

1. **Evaluation of the impact of septoplasty on headache and allergic rhinitis in patients with septal deviation**
2. **Evaluation of association between IL-36 family cytokines in peripheral blood and assessment of subjective and objective results in patients with allergic rhinitis**
3. **Investigation of IL-1β and iNOS in enhancing asthmatic comorbidities and decreasing the lung function in perennial allergic rhinitis children**
4. **Case report on Churg-Strauss syndrome**

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Evaluation of the impact of septoplasty on headache and allergic rhinitis in patients with septal deviation

Septoplasty significantly improved Allergic Rhinitis and symptoms and headaches

Introduction

Nasal septal deviation is the most prevalent condition which has become a major global health issue that impacts approximately 90% of the population. Due to the global prevalence of septal deviation worldwide as well as the rising levels of air pollution the incidence of allergic rhinitis (AR) has increased worldwide, impacting millions of people and interfering with their everyday life, productivity, and work performance.[1] Allergic rhinitis is a chronic inflammatory disease in which the upper airway respiratory mucosa becomes inflamed in response to allergen exposure. Common symptoms include sneezing, rhinorrhoea, nasal congestion, nasal itching and nasal obstruction.[2] Patients frequently suffer headaches as a result of the presence of septal deviation and AR, which might worsen their symptoms. This study aimed to determine the intricate relationship between nasal septal deviation, AR and headaches.

Methods

This was a multicentre, prospective, longitudinal, observational study. It enrolled patients with deviated nasal septum, nasal symptoms, and headaches associated with persistent allergic rhinitis lasting at least 2 months without resolution. A total of 196 patients (102 males and 94 females) were enrolled in the study. The patients had symptoms of severe allergic rhinitis and experienced headaches associated with allergic rhinitis. The severity of allergic rhinitis and different types of headaches in the patients was measured before and after septoplasty. This included evaluating the nasal obstruction using the NOSE scale, Immunoglobulin-E (Ig-E) levels, and visual analogue scale (VAS) for headache pain severity. The impact of septoplasty on allergic rhinitis, headaches, and their types was assessed using the Wilcoxon signed-rank test to compare preoperative and postoperative Ig-E levels, NOSE scale, and VAS scores.

Results

Of the 196 patients, 134 (68%) had been diagnosed with severe RA, and 166 (85%) reported they experienced headaches when they had AR (Figure 1). Of the 166 patients who reported headaches, 100 experienced sinusoidal headaches (or 60% of the total), and 42 had a combination of sinusoidal and migraine headaches (or 25% of the total). A small percentage of individuals (24 out of 166; 14%) had headaches mainly related to migraines. Trouble breathing through the nose and trouble sleeping were the two most commonly reported symptoms of AR, as reported by 57% (112 of 196) and 61% (120 of 196) of the individuals, respectively. After the surgical procedure, there was a consistent decrease in mean NOSE scores for up to 4 months after the procedure and the mean value decreased from 8.52 at 1 month to 2.09 at 4 months (Wilcoxon signed-rank test Z-value of 12.167; $P < 0.001$). Comparably, from the preoperative

to the 4-month postoperative time-point, the levels of Ig-E demonstrated a significant improvement. The subjects' average VAS severity score for headaches was 36.53 before septoplasty. The VAS ratings showed statistically significant improvements after septoplasty wherein, the mean score decreased from 19.08 at 1 month to 12.75 at 4 months (Wilcoxon signed-rank test Z-value of 10.545; P <0.001). Improvement in headache was observed in patients who experienced sinusoidal headaches exclusively, as well as in patient with both sinusoidal headaches and migraines.

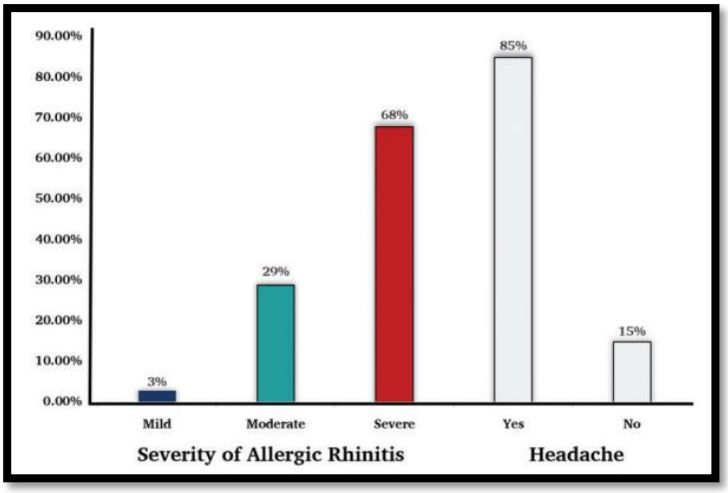

Figure 1. Patients with septal deviation (n=196) having allergic rhinitis associated with headache

Discussion

According to the results of the current study, 85% of patients with septal deviation also reported experiencing headaches, and 68% of patients had severe AR. Globally, mild-to-moderate AR affects 20% to 40% of people, headaches affect 34% of AR patients. The 90% global incidence of septal deviation and the significant increase in air pollution in recent years, which has been linked to AR globally, were additional factors contributing to the disparity. Additionally, the results of this study showed that septoplasty significantly improved patient's symptoms of AR who have septal deviation.[1] Qobty A et al. also reported that septoplasty improved AR symptoms in two-thirds of patient's.[3] This suggested that septoplasty was most beneficial in allergic rhinitis condition especially in patients residing at air polluted countries.

Conclusion

This study showed that individuals with septal deviation who underwent septoplasty experienced a significant reduction in their symptoms of AR and relief from sinusoidal headaches.

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Evaluation of association between IL-36 family cytokines in peripheral blood and assessment of subjective and objective results in patients with allergic rhinitis

Introduction

IL-36α and IL-36β can be used as objective indicators to evaluate the severity of allergic rhinitis

Allergic rhinitis (AR), a common illness that affects 400 million people globally is a cause for concern as it's frequency is rising over time. Typically, AR coexists with other illnesses as asthma, which can have a serious negative financial impact as well as lower quality of life. It has been demonstrated that abnormally high Th2 cytokines are the source of AR, and new research on the cause indicates to a compromise in the integrity of the nasal epithelial barrier.[1] Increasing evidence suggest that the cytokines of the IL-36 family play a major role as mediators in a variety of inflammatory disorders and were closely related to the onset of disease. The peripheral serum of AR patients also contained significantly higher protein concentrations of IL-36 family cytokines than did normal controls, indicating that these cytokines may play a role in the pathophysiology of AR. However, it was unclear whether AR patients' levels of IL-36 family cytokines were related to the severity of their disease.[2] This study was conducted to investigate the correlations between IL-36 family cytokine levels and subjective and objective assessment results and to further examine the potential roles that cytokines from the IL-36 family in the development of AR.

Methods

About 77 patients with AR were included in this study. Inclusion criteria for the study involved patients aged 5 to 70 years with a confirmed diagnosis of allergic rhinitis (AR) and no other respiratory tract or allergic diseases. The 22-item sino-nasal outcome test (SNOT-22) score was used to assess bother-someness problems associated with AR symptoms and quality of life. Severity of illness visual analogue scale (VAS) score was utilized to assess the overall extent of AR symptoms, including nasal, ocular, and asthma-related symptoms. Blood samples were collected from the participants, and the concentration of IL-36 family cytokines was measured using enzyme-linked immunosorbent assay (ELISA). Correlation analysis was conducted to assess the relationship between IL-36 family cytokine concentration levels and VAS scores, SNOT-22 scores, and other clinical parameters.

Results

Patients with AR had the highest concentration of IL-36α, IL-36Ra, IL-36γ, and IL-38 in their peripheral blood, whereas IL-36β had the lowest level (Figure 1). Spearman rank correlation analysis showed IL-36α level was positively correlated with IL-36γ, IL-36β level was

positively correlated with IL-36Ra and IL-38, IL-36γ level was positively correlated with IL-36Ra and IL-36Ra level was positively correlated with IL-38 level. 49 out of 77 AR patients tested positive for total immunoglobulin E (tIgE) allergen, resulting in a 63.64% positive rate (49/77). It was found that IL-36α level was positively correlated with VAS score for nasal congestion symptoms, while IL-36β level was positively correlated with the total VAS score for ocular symptoms and VAS scores for ocular itching and eye pain symptoms. However, it was found that there was no correlation between the levels of all cytokines in IL-36 family and SNOT-22 score, the number of positive inhaled allergens, or the maximum positive intensity of allergen specific immunoglobulin E (sIgE).

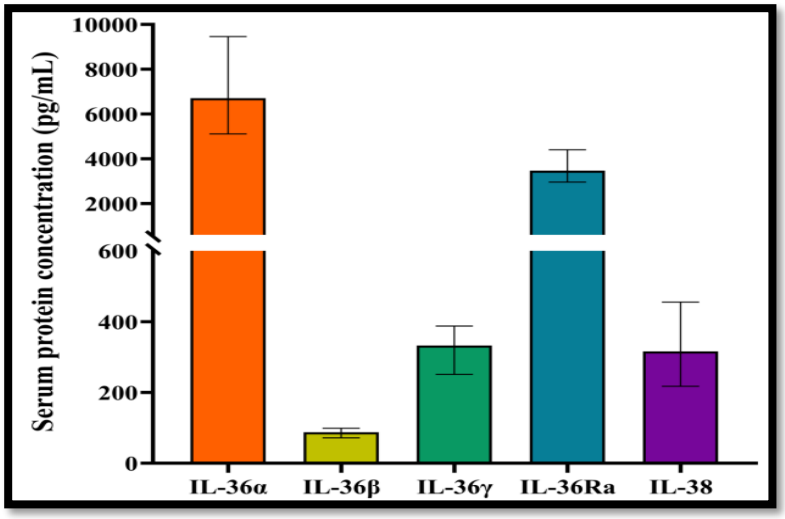

Figure 1. IL-36 family cytokines concentration in the peripheral blood of 77 patients with AR

Discussion

The study's findings demonstrated a weak positive connection (r=0.28, P=0.013) between the levels of IL-36α and IL-36γ in the peripheral blood of AR patients. It also showed that IL-36β level in peripheral blood was moderately correlated with the level of the IL-36R antagonist IL-36Ra (r=0.55, P<0.001). Additionally, there was a weak positive association between the levels of IL-36γ and IL-36Ra in peripheral blood. However, in this study, patients with AR had the lowest levels of IL-36β and the highest level of IL-36α in their peripheral blood.[2] Qin X et al. study reported compared to healthy controls, patients with AR had significantly increased peripheral blood protein concentrations of IL-36α, IL-36β, IL-36γ, IL-36Ra, and IL-38, with IL-36γ having the highest concentration.[3] Thus IL-36α and IL-36β levels were correlated with severity of AR and these could be used as objective indicators to assess the severity of AR.

Conclusion

The results of this study showed a correlation between the severity of the condition of patients with AR and the protein concentration levels of IL-36α and IL-36β cytokines in peripheral blood. As a result, IL-36α and IL-36β may be used as objective markers to assess the severity of AR.

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Investigation of IL-1β and iNOS in enhancing asthmatic comorbidities and decreasing the lung function in perennial allergic rhinitis children

Introduction

Elevated levels of IL-1β, iNOS, and vimentin in the serum were identified as significant indicators of comorbidity of perennial allergic rhinitis and asthma in children.

Asthma is a common chronic inflammatory condition in children and adolescents. Asthma and allergic rhinitis (AR) usually co-exist in same patient, in children as well as in adults. Around 38% of individuals with allergic rhinitis also have asthma, and 6% to 85% of those with asthma also have nasal symptoms.[1] Around 80% of the patients with perennial asthma have AR. Nitric oxide (NO) is an essential regulator of various physiological functions of airway epithelium. Increased levels of NO concentration by dysregulation of iNOS activity enhances chronic inflammatory responses and nitration of proteins which triggers bronchial epithelial tissue injury leading to various pulmonary diseases such as asthma.[2] This study aimed to evaluate the role of interleukin-1β (IL-1β), a pro-inflammatory cytokine, and inducible nitric oxide synthase (iNOS) in comorbidity of AR and asthma and in decline of lung function.

Methods

A nested case control study was conducted in a total of 240 participants with perennial AR (PAR) (PAR alone: 113 children, PAR and asthma: 127 children). Study included only PAR children, having an inflammatory process all year round. Diagnosis of AR was made on the basis of symptoms such as rhinorrhoea, nasal obstruction, nasal itching, and sneezing and objective tests of IgE-mediated allergies, such as the skin prick test. The enzyme-linked immunosorbent assay (ELISA) was used to evaluate serum levels of IL-1β (which indicates the activation of inflammasomes), CCL-24 (chemokines that produce eosinophils in allergic disorders) and the EMT marker. Furthermore, a NOS kit was used to measure the epithelial iNOS data. The study employed univariate and multivariate analyses to investigate potential associations between various variables and the onset of comorbidity and decreased lung function.

Results

Total IgE, eosinophil count, and vimentin did not vary significantly between the PAR alone group and the PAR and asthma group. The PAR and asthma group had significantly greater levels of IL-1β, CCL24, and iNOS, whereas E-cadherin was significantly lower. In both groups, Dermatophagoides pteronyssinus or Dermatophagoides farina had the highest number of positive allergies. Univariate analysis showed that IL-1β (>10.84 pg/ml), iNOS (>43.63 pg/ml), and vimentin (>486.0 pg/ml) were associated with the development of comorbidity of

PAR and asthma (p= 0.003, 0.038 and 0.005, respectively), whereas according to multivariate analysis elevated levels of IL-1β (5.6- fold increase in risk) and high expression of iNOS and vimentin (6.3 and 7.9-fold increase in risk) were the significant risk factors for the development of comorbidity of PAR and asthma. Significantly higher levels of IL-1β, iNOS, and vimentin were seen in the group with decreased lung function (n=113) compared to the normal PFT (n=126). Decreased lung function was associated with IL-1β (>10.84 pg/ml), iNOS (>43.63 pg/ml), and vimentin (>486.0 pg/ml) in univariate analysis (p=0.027, <0.001, and 0.020, respectively). High expression of iNOS and vimentin (22.3 and 6.7-fold increase in risk), as well as elevated IL-1β (7.8-fold increase in risk), were found to be significant risk factors for the development of decreased lung function in multivariate analysis. Strongest risk factor for comorbidity and decreased lung function was elevated levels of iNOS. Vimentin or CCL-24 activation by IL-1β or iNOS can independently cause comorbidity or a decrease in pulmonary function in AR.

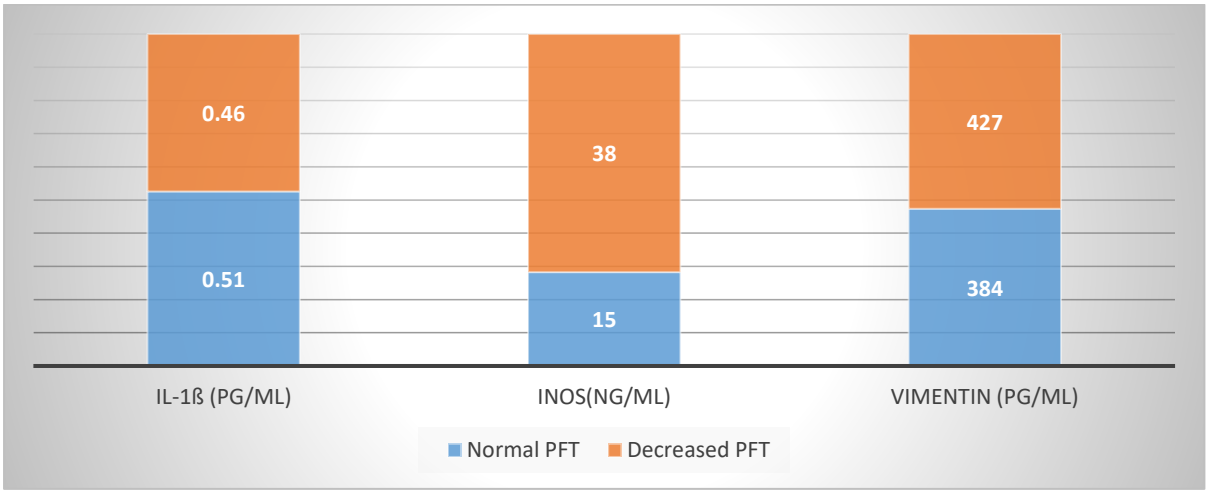

Figure 1. Biomarkers expression in normal lung function and decreased lung function groups

Discussion

This investigation found that children with greater IL-1β levels had an increased risk of AR and asthma comorbidity and decreased lung function.[2] Han MW et al. also showed that activation of IL-1β, a pro-inflammatory cytokine, might be a risk factor for moderate perennial AR and worsening of AR symptoms.[3] Furthermore, it has been determined that vimentin, a marker of airway remodelling, poses a risk for both comorbidity and decreased lung function. Moreover, in children with persistent AR, increasing IL-1β was linked to increased vimentin expression, indicating that IL-1β may initiate airway remodelling when comorbidity develops by activating vimentin. Based on its association with CCL, the study data suggested that iNOS can be a risk factor for the comorbidity of asthma and PAR as well as decreasing lung function. In children with persistent AR, iNOS and IL-1β can both independently decrease lung function or cause comorbidity through interacting with airway remodelling biomarkers.[2]

Conclusion

According to this study, IL-1β and iNOS can be biomarkers in the development of PAR and asthma and decreased lung function, indicating possible areas for early detection and therapy.

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Case report on Churg-Strauss syndrome

Introduction

Churg-Strauss syndrome is mainly characterized by vasculitis accompanied by eosinophilia, which affects the respiratory system.

Churg–Strauss syndrome (CSS) also known as eosinophilic granulomatosis is a rare disease characterized by systemic vasculitis involving primarily the small and medium-sized arteries and veins. CSS is associated with peripheral eosinophilia and asthma and it affects two or more extra pulmonary organs.[1] American College of Rheumatology proposed six criteria for diagnosis of CSS which includes asthma, paranasal sinusitis, eosinophilia (>10% in peripheral blood), pulmonary infiltrates, histological proof of extravascular eosinophil infiltration, and mononeuritis multiplex or polyneuropathy. When four of these criteria are met, there is a strong likelihood of a CSS diagnosis. Nearly 98% of patients with CSS have asthma.[2] This report presented a case of Churg-Strauss syndrome.

Case Presentation

A 51 years old female patient with history of cough since past 1 month and complaint of newly developing bloody sputum. Patient was on treatment with inhaled corticosteroid therapy and montelukast + antihistamine therapy for asthma. However, patient had dry cough that persisted even after using two cycles of antibiotics for the past several months. The patient's laboratory tests revealed the following information: leukocyte count on peripheral smear: 9.000/mm3, eosinophil count: 1.500/mm3, haemoglobin level: 10.7 g/dL, hematocrit level: 34%, platelet count: 413.000/mm3, C-reactive protein 8.64 mg/L, glucose 89 mg/dL, glycated haemoglobin A1c (HbA1c) 5.8%, BUN 12 mg/dL, creatinine 0.9 mg/dL, total protein 7.9 g/dL, total bilirubin 0.4 mg/dL, albumin 4.9 g/dL, cholesterol 192 mg/dL, triglyceride 104 mg/dL, uric acid 27 mg/dL, ALT 10 IU/L, AST 17 IU/L, ALP 67 IU/L, GGT 17 IU/L, LDH 361 IU/L, and IgE 699

IU/mL.The ear, nose, and throat exam and paranasal CT revealed chronic sinusitis and nasal polyps. Low lung ventilation was seen in the lower left on the chest X-ray (Figure 1). On the basal segment of the left lobe, a nodular mass with a diameter of about 4 cm was visible on a CT scan of the thorax, next to the diaphragm. PET-CT revealed involvement favouring malignancy in the mass. The patient was advised to undergo video-assisted thoracic surgery (VATS). A biopsy performed with VATS revealed leukocytoclastic vasculitis with evident eosinophils and pulmonary infarction. Rheumatology and vasculitis were identified as the patient's conditions. Methylprednisolone (MP) was started at 1 mg/kg/day and azothioprine (AZT) at 2 mg/kg/day. After 3 and 6 months of starting the treatment, it was observed that all clinical and radiological findings disappeared. Treatment with 8 mg/day MP and 100 mg/day AZT was continued. In the 18th month of treatment, the patient was readmitted

with a cough complaint. After the patient

had additional investigations, a newly developed pericardial effusion was found. The MP and AZT dosages were increased on a rheumatologist's advice. The medication

was supplemented with colchicine.

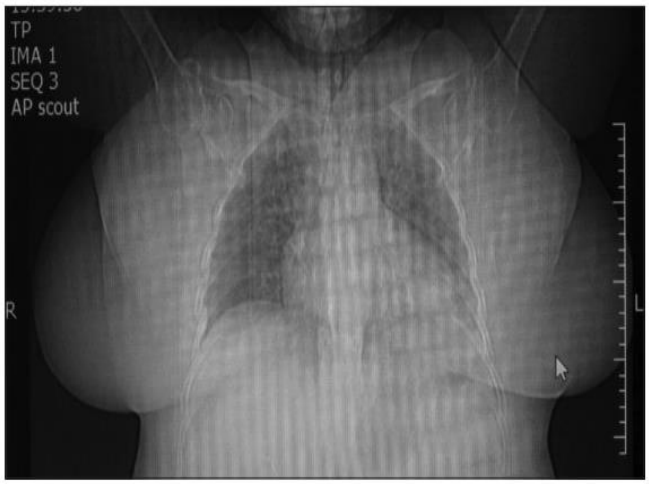

Figure 1. Chest x-ray of lower left showing low lung ventilation

During the patient's follow-up, the pericardial effusion was found to have totally resolved, and the coughing episode was under complete control.

Discussion

CSS affects small and medium vessels and causes blood and tissue eosinophilia and severe asthma. This report is mainly defined by eosinophilia, an illness that affects the respiratory system, along with vasculitis. Vasculitis in this report included asthma, peripheral blood eosinophilia, paranasal sinusitis, pulmonary infiltration and extravascular eosinophils in pulmonary tissue. The three important criteria in this case were the history of asthma, greater than 10% eosinophilia, and allergy. [1] According to a study, those who test negative for ANCA were more likely to develop cardiac disease.[3] Additionally, this patient's ANCA was found to be negative. Reduced dosages of MP and AZT caused cardiac involvement to manifest as pericardial fluid. On the other hand, pericardial fluid could be brought under control by increasing medication dosages. The organ most frequently involved in CSS is the lung.[1] One of the 6 ACR criteria used in the diagnosis of CSS was pulmonary infiltration, which was present in around 90% of patients.[3] Rheumatic complaints, including myalgia and arthralgia, which this case patient also experienced, have been shown in several case studies to occur in half of CSS patients and to be most common during the vasculitic phase of the disease.[4]

Conclusion

This report highlighted the importance of considering lung vasculitic disease, particularly CSS, while treating patients with asthma who also have uncontrollable hemoptysis or a cough.

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