THE CLINICAL AND RADIOLOGICAL CHARACTERIZATIONS OF ALLERGIC PHENOTYPE IN CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

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ABSTRAK

Objektif: Fenotip alahan memainkan peranan sebagai subset kronik rhinosinusitis dengan polip (CRSwNP) dan tanpa polip (CRSsNP) baru baru ini. Kami ingin menerangkan ciri-ciri klinikal dengan penilaian simptom dan skor endoskopik dan radiologi dengan skor Lund Mackay pesakit dengan fenotip alahan di kalangan pesakit CRSwNP. Kajian ini penting untuk menentukan perkaitan antara alahan dan CCAD dengan CRSwNP yang akan membantu pemahaman panyakit dan seterusnya membantu merawat pesakit pesakit sewajarnya.

Methodologi: Kajian keratan rentas dijalankan pada pesakit CRSwNP yang menjalani kedua-dua penilaian alahan dan penilaian radiologi. Keseluruhan skor gejala nasal termasuk3 masalah rhinologi yang berkaitan dengan alahan (kehendak untuk menghembus hidung, bersin, dan hidung berair), skor endoskopi Lund Kennedy (LK), skor pemeriksaan imbasan tomografi (CT) sinus hidung (PNS) Lund Mackay (LM), ciri-ciri central compartment atopic disease (CCAD), ujian cucuk kulit dan tahap IgE specifik telah dinilai.

Keputusan: Tiada perbezaan dalam skor simptom secara keseluruhan tetapi simptom alahan lebih tinggi dalam kumpulan atopy dan CCAD. Terdapat perbezaan yang ketara

dalam skor endoskopik dan skor CT PNS antara atopy dan bukan atopy serta CCAD dan bukan CCAD. CCAD mempunyai kaitan yang ketara dengan atopy dan mempunyai skor endoskopik dan CTPNS yang lebih tinggi.

Kesimpulan: Atopy dan fenotip radiologinya, CCAD mesti dinilai dengan betul pada pesakit dengan CRSwNP kerana ini menentukan keterukan klinikal dan radiologi pesakit. Pesakit dengan atopy dan CCAD mempunyai lebih banyak perubahan turbinat tengah kepada polip, skorsimptom, endoskopik dan CTPNS yang lebih tinggi yang membuktikan bahawa adanya perkaitan antara alahan dan CRSwNP.

ABSTRACT

Objectives: Allergic phenotype has recently been described as a subset of chronic rhinosinusitis with polyps (CRSwNP) and without polyps (CRSsNP). Our aim is to explain the clinical characterizations with symptoms and endoscopic Lund Kennedy scoring as well as radiological characterizations with Lund Mackay scoring of patients with the allergic phenotype of CRSwNP. The importance of this study is to determine the association of allergy and CCAD to CRSwNP that will aid in further understanding of the pathophysiology of the disease and managing the patients accordingly.

Methods: A cross-sectional studyon patients diagnosed with CRSwNP who had both allergology and radiological assessments. Theoverall nasal symptoms score including 3 rhinologic problems, with relevance to allergy (need to blow nose, sneezing, and runny nose), Lund Kennedy (LK) endoscopic scoring, Lund Mackay (LM) scoring of computed tomography (CT) scan of the paranasal sinuses (PNS), central compartment atopic disease (CCAD) features, skin prick test (SPT) and level of specific IgE were assessed.

Results: There was no difference in overall symptoms score but there was a higher allergy symptoms burden in atopy and CCAD groups. There was significant difference

in the endoscopic and CT PNS scores between atopy and non-atopy as well as CCAD and non CCAD. CCAD has a significantly association with atopy and has a higher endoscopic and CT PNS scores.

Conclusions: Atopy and its radiological phenotype, the CCAD must be properly assessed in patients with CRSwNP as they may determine the clinical and radiological severity. Patients with atopy and CCAD have more polypoidal involvement of the middle turbinates, additional symptoms burden and higher endoscopic and CT PNS scoring proving that there is an association between allergy and CRSwNP.

Chapter 1:

INTRODUCTION

1.1 INTRODUCTION

Chronic rhinosinusitis (CRS) is a complex disease with significant socio-economic impact causing a public health problem. This disease has a heterogenous nature of pathophysiology causing different variants of the disease thus limiting our understanding on the causes of CRS and the directions for most appropriate targeted treatment strategies.

CRS is clinically divided into two main subtypes : CRS with nasal polyp (CRSwNP) and CRS without nasal polyp (CRSsNP).

CRS, with or without nasal polyps is defined as inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/congestion or nasal discharge (anterior/posterior nasal drip), and/or facial pain/pressure, and/or reduction or loss of smell for more than 12 weeks. This should be supported by computed tomography (CT) scan showing mucosal changes in the ostiomeatal complex or the sinuses or by endoscopic assessment showing nasal polyp and/or mucopurulent discharge, and/or oedema with mucosal obstruction primarily in the middle meatus.

Paranasal sinusmucosal changes are objective diagnostic criteria for CRS and the changes can be evaluated by computed tomography of paranasal sinus (CTPNS). Despite its diagnostic value, CT also assist in evaluating the efficacy of medical and surgical therapy for CRS by using a proposed summarized scoring method such as Lund Mackay. The ultimate aim of this scoring method is to develop an association between the radiological features and other findings such as severity of symptoms and efficacy of treatment and further improving and achieving adequate therapy for patients.

Besides the Lund Mackay scoring, the radiologically seen mucosal oedema was also described by the central compartment atopic disease (CCAD) radiological phenotype. The changes due to allergic reaction in the nose causing obstruction involving the middle turbinates, superior turbinates and postero-superior part of the septum is defined as CCAD.CCAD was developed to recognize the role of aeroallergen as one of the causes of allergic phenotype of chronic rhinosinusitis.

The definition of atopy varies in the literature and sometimes used interchangeably with allergy. In general, most would agree that atopy is a tendency to produce IgE to allergens and is a characteristic phenotype of diseases such as AR or as a disease modifier.

Atopy has long been one of the proposed etiological factors in pathogenesis of nasal polyps and strongly associated with worsening of symptoms in CRSwNP.Failure to recognize and treat this association may result in recurrences, increased morbidity and poor treatment outcome.

Skin prick testing (SPT) is an essential test procedure to confirm sensitization in IgE- mediated allergic disease in subjects with rhinoconjunctivitis, asthma, urticaria, anaphylaxis, atopic eczema, food and drug allergy.The recommended method of skin prick testing includes the appropriate use of specific allergen extracts, interpretation of the tests after 15 – 20 minutes of application, with a positive result defined as a wheal ≥3 mm diameter(1).

Immunoglobulin E (IgE) holds a unique position among all immunoglobulins. It is normally present in human serum in extremely small amounts and may increase

several hundred fold in response to specific stimuli such as in allergic diseases like allergic rhinitis, bronchial asthma and atopic dermatitis.Quantifying IgE antibodies with ImmunoCAP Specific IgE results in accurate evaluation of allergy patients.

Chapter 2:

OBJECTIVES OF THE STUDY

2.0 OBJECTIVES OF THE STUDY

2.1 General objectives

- To determine the disease burden in CRSwNP and its association withatopy.

2.2 Specific objectives

- To describe the severity of symptoms in CRSwNP via visual analoguescale.
- To describe the severity in CRSwNP via Lund Kennedy score of endoscopic assessment.
- To describe the severity in CRSwNP via Lund Mackay score of CTscan.
- To determine the association between atopy and severity of CRSwNP in Lund Mackay score and CCAD system of CT scan.

Chapter 3:

MANUSCRIPT

3.1 TITLE PAGE

The clinical and radiological characterizations of allergic phenotype of chronic rhinosinusitis with nasal polyps

Running title:Allergic phenotype of chronic rhinosinusitis with nasal polyps

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3.2 ABSTRACT

Introduction

Allergic phenotype has recently been described as a subset of chronic rhinosinusitis with polyps (CRSwNP) and without polyps (CRSsNP). Our aim is to explain the clinical characterizations with symptoms and endoscopic Lund Kennedy scoring as well as radiological characterizations with Lund Mackay scoring of patients with the allergic phenotype of CRSwNP. The importance of this study is to determine the association of allergy and CCAD to CRSwNP that will aid in further understanding of the pathophysiology of the disease and managing the patients accordingly.

Methods

A cross-sectional comparative studywas done on patients diagnosed with CRSwNP who had both allergology and radiological assessments. The overall nasal symptoms score including 3 allergic related rhinological problems, (sneezing, need to blow nose, and runny nose), Lund Kennedy (LK) endoscopic scoring, Lund Mackay (LM) scoring of computed tomography (CT) scan of the paranasal sinuses (PNS), central compartment atopic disease (CCAD) features, skin prick test (SPT) and the specific IgE level were assessed.

Results

There was no difference in overall symptoms score but there was a higher allergy symptoms burden in both the allergy and CCAD groups. There was a significant difference in the endoscopic and CT PNS scores between the allergy and non-allergy as

well as CCAD and non CCAD. CCAD had a significant association with allergy and a higher endoscopic and CT PNS scores.

Conclusions

Allergy and its radiological phenotype, the CCAD must be properly assessed in patients with CRSwNP as they may determine the clinical and radiological severity. Patients with allergy and CCAD have more polypoidal involvement of the middle turbinates, additional symptoms burden and higher endoscopic and CT PNS scoring proving that there is an association between allergy and CRSwNP.

Key Words: Atopy;Allergy; Chronic rhinosinusitis; Symptoms; Endoscopy;Computed tomography

3.3 INTRODUCTION

Chronic rhinosinusitis (CRS) is inflammation of the nose and the paranasal sinuses distinguished by two or more symptoms, one of which should be either nasal discharge (anterior/posterior nasal drip) or nasal blockage/congestion, and/or facial pain/pressure, and/or reduction or loss of smell for more than 12 weeks according to the European position paper on rhinosinusitis and nasal polyps (EPOS) guidelines [1]. This should be supported by computed tomography (CT) scan of the paranasal sinuses (PNS) showing mucosal changes in the sinuses or the osteomeatal complex or by endoscopic assessment showing nasal polyp and/or oedema with mucosal obstruction particularly in the middle meatus, and/or mucopurulent discharge [1, 2]. The central compartment atopic disease (CCAD), aradiological phenotype in allergic patients has recently been described [3].CCAD describes the changes due to allergic reaction in the nose causing obstruction involving the middle turbinates, superior turbinates and postero-superior part of the septum.CCAD was developed to recognize the role of aeroallergen as one of the causes of allergic phenotype of chronic rhinosinusitis [3].

Allergy has long been one of the proposed etiological factors in pathogenesis of nasal polyps but its role in CRS is still unsettled [4,5]. Most studies used multiple allergens to confirm allergy in CRS patients with polyps (CRSwNP) or without polyps (CRSsNP). As it is often considered as one disease entity, the same considerations were applied for CRSwNP and CRSsNP. However, CRSwNP should be considered as a distinct entity due to differences in its inflammatory mediators from CRSsNP [6]. CRSsNP is a TH1 shifted immune response with predominance of mono-nuclear cells and interferon

gamma in the nasal tissue, whereas CRSwNP is a TH2 dominated disease with predominance of interleukin 5 and eosinophils [7]. Thus, their mechanism of response to multiple allergens might not be the same. CRSwNP is characterized predominantly by eosinophilic inflammation and local IgE production, that can suffer from inhalant allergy with different response to allergens, thus CRSwNP was specifically included in this study. Their diverse nature and heterogeneous pathophysiology explains the variation and contradictory results in prior studies. The standardization of the predominant allergen and the type of CRS, a more reliable and predictive response could be elucidated. We aim to describe the clinical and radiological characterizations of patients with the allergic phenotype of CRSwNP.

3.4 METHODOLOGY

This was a cross sectional comparative study conducted within one year of duration from June 2018 to June 2019 on patients diagnosed with CRS who underwent allergology and radiological assessments. Prior approval from the local human research ethics committee (JEPeM Code: USM/JEPeM/17120676) was obtained for the study and written informed consent was taken from all participants.

Study population

All patients above age of 18 diagnosed with CRSwNP according to the European position paper on rhinosinusitis and nasal polyps (EPOS) guidelines from Otorhinolarynogology clinic, University Sains Malaysia Hospital were included in this study. Patients who had previous surgery or with history of fungal rhinosinusitis and mucocele were excluded from this study. Demographic data including age, gender, smoking habits, presence of systemic diagnoses in addition to a history of bronchial asthma were obtained from patients. The use of intranasal corticosteroid or oral steroid were documented. The allergy status was first assessed via skin prick test (SPT) and specific IgE level followed by the symptoms scoring, Lund Kennedy (LK) endoscopic scoring, and Lund Mackay (LM) CTPNS scoring.

Allergy status

Clinical history for allergy and atopy was obtained from all patients prior to SPT. The history includes the three rhinological symptoms related to allergy namely sneezing, runny nose and the need to blow the nose [3]. These symptoms were scored on a scale of 0 to 5 (0 = no problem, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe and 5 = worst). SPT was done on each patient before treatment or 2 weeks after refraining from oral or topical steroid and oral anti-histamine[8]. SPT was performed on the patient's volar forearm using the two most common inhalant allergens in our patients, thedermatophagoides and blomia tropicalis [9]. Histamine was used for positive control and saline for negative control. Patients with a positive skin test result that was presented as a wheal size of more than 3 mm to allergens and a nonreactive negative control after 15 minutes were grouped as allergy.Patient with wheal size of less than 3 mm with positive allergy and atopy history underwent venous blood taking to determine the level of serum specific IgE to dermatophagoides and blomia tropicalis (analyzed via ImmunoCAP, Phadia AB, Uppsala, Sweden). A value of 0.35 KU/L or more of the serum specific IgE was considered positive for allergy.

Symptoms assessment

Symptoms of rhinorrhea, nasal congestion, nasal obstruction,hyposmia,post nasal drip, facial pain or fullness and headache were evaluated, and the overall total symptoms scored according to the visual analogue scale (VAS) from score 0 to 10. Three allergic related rhinologic problems, (sneezing, need to blow nose, and runny nose) scored on scale of 0 to 5 (0-no problem, 1-very mild problem, 2-mild or slight problem,

3-moderate problem, 4-severe problem, and 5-problem bad as can be) were further described.

Endoscopic assessment

LK endoscopic scoring system was used to evaluate the nasal endoscopic findings [10]. The scoring was as follows: size of polyps (0=none, 1=till middle meatus, 2= extend beyond middle meatus), oedema of the turbinates (0=absent, 1=mild to moderate oedema, 2=polypoidal degeneration) and discharge (0=none, 1=clear and thin, 2=thick and purulent) with a possible total score of 12.

Radiological assessment

The CTPNS was retrieved from radiology information system (RIS) and picture archive communication system (PACS). The CTPNS images were obtained from SOMATOM ® Definition AS+ (Siemens Healthcare GmbH, Germany) which can construct 128 slices of images per rotation. The paranasal sinuses were reviewed from serial images (1 mm slices) on axial, coronal, and sagittal views on both right and left side. CT PNS done within 3 months prior or after allergic assessment was included to explain the correlation between the most recent CT findings and the current allergy results. The CT PNS images were reviewed and classified according to LM scoring system [11] by an

otorhinolaryngologist who was blinded to the allergy status. The LM scoring assigns a score of 0, 1 or 2 to each sinus (maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal) and a score of 0 or 2 for each osteomeatal complex with a possible total score of 24. A score of 0 is assigned for a well aerated sinus, 1 for partially opacified sinus and score of 2 is designated for a completelyopacified sinus. In reference to the osteomeatal complex,0 is assigned if its unobstructed and 2 is assigned if obstruction present. The CCAD features were classified according to previous works done by Delgaudio et al. [12] and Aneeza et al. [3]. Centrally limited disease was defined by normal sinus mucosa or mucosal thickening involving the floor and medial wall of the sinus (Figure 1). The diffuse disease was defined as mucosal thickening involving all 4 walls of the sinus or involving the lateral wall and the roof of the sinus.

Statistical analysis

Sample size was calculated using Power and Sample Size Program.A total of 38 samples (19 atopy and 19 non-atopy) was required for this study to achieve significant with true failure rate for experimental subjects as 0.5, probability (power) of 0.8, type I error probability associated with test of null hypothesis via uncorrected chi-squared statistic as 0.05 and prevalence was based on reference to Aneeza et al.[3]. Data was entered and analyzed using SPSS version 22. Descriptive statistics was used to summarize the socio-demographic characteristics of subjects, VAS symptoms severity, LK endoscopic and LM CTPNS scoring in CRSwNP. Numerical data presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data was presented as frequency (percentage). Mann-Whitney test was used to determine the

association between allergy and severity of CRSwNP in LM CTscoring as the normality assumption was violated. Pearson Chi Square test was used to determine the association between allergy and CCAD.A value of $p < 0.05$ was accepted as the significance level.

3.5 RESULTS

Participant characteristics

There was a total of 38 patients with CRSwNP recruited in this study; 19 patients with allergy and 19 patients without allergy. Table 1 shows the characteristics of the allergy and non-allergy populations. The mean age for the allergy group was 47.8 + 17.3 with a predominance of male (68.4 %) while for the non-allergy group, the mean age was 52.8 + 14.9 and a predominance of female (52.6 %). In the allergy group of patients, we found 68.4 % of patients were allergic to both dermatophagoides and blomia tropicalis, and the rest were allergic to blomia tropicalis only. 26.3 % of patients in the allergy group had bronchial asthma as compared to 21.1 % of patients in the non-allergy group. The use of intranasal steroid spray was 100 % for both allergy and non-allergy groups. The use of oral steroid was higher in the allergy group (63.2 %) in comparison with the non-allergy group (36.8 %).

Table 2 shows characteristics of the central compartment atopic disease radiological pattern. There was a total of 16 patients that had CCAD features on CT PNS with mean age of 49.38 $\pm$ 16.9 and a male predominance (62.5 %). In the CCAD group, 25 % of patients had bronchial asthma. None of these patients were documented to have aspirin or NSAID hypersensitivity. The use of intranasal steroid spray was 100 % for both CCAD and the non CCAD groups, where else the use of oral steroid was higher in the CCAD group (68.8 %) in comparison with the non CCAD group (36.4 %).

There was a total of 9 patients with bronchial asthma out of the 38 patients and out of this 9 patients, 55.6 % were positive for allergy and 44.4 % had CCAD pattern on CT PNS.

Symptoms severity in allergy and CCAD groups

The mean VAS in the allergy and non-allergy groups is as shown in Table 1. The mean VAS in the CCAD and non CCAD groups is as shown in Table 2. Table 3 explains the individual rhinologic score, % moderate problem or more. The symptoms of need to blow nose and sneezing, were higher in the allergy group when compared to the non-allergy group. The symptom of runny nose was the same for both allergy and non-allergy groups. For the CCAD group, the symptoms of need to blow nose and sneezing showed higher incidence as compared to the non CCAD group. The symptom of runny nose was the same for both CCAD and the non CCAD group.

Endoscopic scoring in allergy and CCAD groups

There was a significant difference in the LK endoscopic scoring between both allergy and the non-allergy groups (Table 1). When CCAD group was compared to the non CCAD group, there was a significant difference in LK endoscopic score (Table 2). Table 4 shows the middle turbinate characteristics of the CCAD and non CCAD. The

middle turbinate changes showed the CCAD group had worse scoring in edema and polypoidal degeneration for both sides compared to the non CCAD group.

Lund Mackay scoring in allergy and CCAD groups

There was a significant difference in LM CT PNS scoring between the allergy and the non-allergy groups (Table 1). A significant difference was also shown between the CCAD and the non CCAD groups (Table 2).

3.6 DISCUSSION

Sedaghat et al. reported that in children with AR and CRS, the prevalence of sensitization for both outdoor and indoor aeroallergens was high and almost similar to the general population of children with AR as well as adult with both AR and CRS [13]. Among these aeroallergens, house dust mites were the most common indoor aeroallergens. In our study, we chose house dust mites as it is the most common allergen in our population.

Several studies stated that disease severity in CRS patients was not associated with the presence of allergy and CTPNS changes have poor correlation with allergy. [14-21]. In investigating the role of atopy in CRS patients, Li et al. found that 47 % of their patients had atopy but the disease severity and recurrence rates were the same, irrespective of the atopic status [14].When the presence of atopy was related to the findings of CT PNS, Erbek et al. and Peric et al. found that there was no association between allergy with both endoscopic findings and LM score in their respective studies [15,16].Pearlman et al. found there was a 52 % of atopy in their patients but no difference in the LM score between the atopy and non-atopy groups [17].In another study, Banerji et al reported there was no difference in CTPNS severity score based on atopic profiles of their patients [18]. Similarly, Tan et al demonstrated in their study there was no difference between CTPNS LM severity and allergic status [19]. Moreover, Basu et al. and Brook et al reported that LM CT PNS severity in CRS patients did not correlate with symptom severity and allergen sensitization respectively [20, 21].

In contrast, the results of our study demonstrated an association between allergy and CRSwNP; the allergy group of patients had worse endoscopic and CT PNS scores in comparison to the non-allergy group. These was demonstrated on Table 1 where the mean $\pm$ SD value for the allergy group was worse with values of 5.58 $\pm$ 2.71 and 14.32 $\pm$ 8.04 respectively for Lund Kennedy and Lund Mackay scoring compared to the non allergy group with values of 3.42 $\pm$ 1.64 and 8.53 $\pm$ 6.24 respectively. There was a significant p value of 0.01 and 0.02 respectively for Lund Kennedy endoscopic score and Lund Mackay CT score that shows there is an association between allergy and CRSwNP. These findings were similar to the study by Ramadan et al. that found their patients with allergy had higher CTPNS scoring compared to those without allergies [5]. Interestingly, Emanuel et al. showed although majority of CRS patients had allergic sensitization, but it did not correlate with the severity of CTPNS scoring [22]. In another study, Yacoub et al. reported that atopy, clinical allergy, asthma and NSAIDS hypersensitivity could play a role in CRS [23]. Krouse et al found allergic sensitization influenced the severity of symptoms in CRS patients but not the severity of the CT PNS scoring [24]. A recent study by Ho et al [25] showed CRS patients with comorbid allergy had additional symptoms burden and they recommended every CRS patient assessed for atopy to ensure proper treatment. Similarly, in our patients we found allergy patients have higher allergy symptoms specifically the need to blow nose and sneezing; although, the overall nasal symptoms score showed no difference between allergy and non-allergy patients.