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Article

Radiological Assessment of Centrally Limited Sinus Disease in Allergic and Non-Atopic Chronic Rhinosinusitis

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Abstract: Background: A centrally limited radiological pattern, marked by mucosal thickening in the central sinonasal cavity with relatively unaffected surrounding sinuses, has been linked to allergy in chronic rhinosinusitis (CRS). However, a comparison between allergic and non-atopic CRS patients is lacking. The role of anatomical variations in the ostiomeatal complex also remains unclear. Methods: Adult CRS patients with allergic rhinitis, asthma, eczema, and positive allergy tests were recruited. CRS patients without atopic disease and negative allergy tests were controls. CT scans were evaluated for the centrally limited radiologic pattern. Anatomical variations in the ostiomeatal complex were also examined. Results: The study included 15 allergic CRS and 17 non-atopic CRS participants. Allergic CRS patients showed a higher prevalence of centrally limited sinus disease compared to non-atopic CRS patients (50% vs. 14.7%, $p < 0.01$). No anatomical variations were conclusively linked to allergy status or the centrally limited sinus disease. Conclusion: Centrally limited sinus disease on radiology is associated with underlying allergy in CRS but should not be the primary diagnostic tool. Anatomical variants did not clearly relate to allergy status or the radiologic pattern but this requires further studies.

Keywords: chronic rhinosinusitis; atopic; phenotype; central compartment atopic disease; central radiological pattern; central mucosal thickening

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1. Introduction

Chronic rhinosinusitis (CRS) is an inflammation of the nose and paranasal sinuses that adversely affects quality of life and increases medical costs worldwide. The etiology of CRS is complex and likely multifactorial, resulting in a dysfunctional interaction between sinus mucosa and the environment [1]. The interaction between aeroallergen and nasal mucosa is proposed as an etiology of CRS. Del Gaudio et al. described a phenotype of CRS driven by inhalant allergies termed Central Compartment Atopic Disease (CCAD) [2]. CCAD is diagnosed in CRS patients with symptoms of allergic rhinitis confirmed by a positive skin prick test and nasal endoscopic finding of polyps involving the central nasal compartment (superior nasal septum, middle, and/or superior turbinate) [3]. These polyps lead to CRS by obstructing the ostiomeatal complex (OMC) [4]. Diagnosis typically involves a history of long-standing allergic rhinitis and nasal endoscopy revealing polyps originating from the middle turbinate, upper septum, or superior turbinate. This is then supported by a centrally limited radiologic pattern on computed tomography (CT) scan, characterized by mucosal thickening in the central nasal cavity and ethmoid sinuses, with minimal involvement of the maxillary, frontal, and sphenoid sinuses [5]. While this centrally limited

radiological pattern can aid in identifying allergic CRS, it is not the main tool for diagnosing this condition [6]. Previous studies that examined this radiologic feature relied on standard allergy tests to define allergy, but a positive test may not be clinically relevant in the nose. The influence of allergy in the development of this central radiological pattern would be better understood if studied among clinically allergic patients with CRS compared to those where allergy has been systematically ruled out.

Apart from that, other factors that may influence OMC drainage should be explored. Anatomical variations of the OMC may narrow the sinus opening, further impairing sinus drainage in the allergic patient. These anatomical variants include concha bullosa, paradoxical middle turbinate, Haller cell, and an everted uncinate process [7]. These variations have been associated with sinus inflammation [8] but their influence on the development of central radiologic patterns among allergic CRS is not well understood. This has management implications, as anatomical variation generally warrants surgery [9].

This study aims to compare the centrally limited sinus disease radiologic pattern between well-selected allergic CRS patients and those with non-atopic CRS. Additionally, anatomical variations in the ostiomeatal complex (OMC) are assessed and compared between the CRS groups, and their association with the central radiologic pattern is explored. The findings will contribute to a more precise approach to diagnosing and managing allergic CRS, helping clinicians implement targeted treatments and improve patient outcomes.

2. Materials and Methods

This was a case-control study conducted at the Otorhinolaryngology outpatient clinic in a tertiary medical center. Approval by the human research ethics committee was obtained prior to the commencement of the study and written informed consent was taken from all the recruited patients (Ethics approval number: JEP-2020-125).

2.1. Study Population

Adult CRS patients (>18 years old) were consecutively recruited and screened for both inclusion and exclusion criteria. Diagnosis of CRS was made when patients fulfilled the criteria based on the European Position Paper on Rhinosinusitis and Nasal Polyps [1]. All involved participants had a prior available computed tomography (CT) scan. Patients were recruited into either the allergic CRS group or the non-atopic CRS group. Patients in the allergic CRS group must have allergic rhinitis symptoms with asthma and eczema. They also must have either a positive skin prick test and/or serum-specific IgE towards at least one aeroallergen. Patients were included in the non-atopic CRS group if they were diagnosed as CRS but without reactive nasal symptoms suggestive of allergic rhinitis. Atopy must have been ruled out by either a negative skin prick test and/or serum-specific IgE. They were excluded from this group if they had any reactive nasal symptoms such as sneezing upon aeroallergen exposure or if they complained of nasal itchiness. They were also excluded from the control group if there was any history of physician-diagnosed asthma or eczema, or any prior use of bronchodilators. CRS patients who did not fulfill either of these group criteria were not recruited. Patients were also excluded from both groups if they had previous sinonasal surgery, fungal rhinosinusitis, aspirin-exacerbated respiratory disease, skull base or facial trauma, sinonasal malignancy, and pregnancy.

2.2. Allergy Tests

The skin prick test (SPT) was conducted which included Dermatophagoides pteronyssinus (DP), Dermatophagoides farina (DF), Blomia tropicalis (BT), cockroach, cat, mixed grass, rye grass, Bermuda grass, Aspergillus, Alternaria, Penicillin and Cladosporium herbarum. We used 50% glycerin as negative control and histamine as positive control. After 15 min of allergens application, the size of the wheal was measured. The result of the skin prick test was defined as positive if the wheal diameter was 3 mm or more.

Serum-specific IgE (sIgE) was measured for the same aeroallergens as the skin prick test by automated immunoassay (Phadia™ 100 instrument, Thermo Fisher Scientific, Waltham, MA, USA). A value of 0.35 kuA/L or more for any tested allergens was considered a positive result for serum-specific IgE.

2.3. Definition of Allergic Co-Morbidities

Allergic rhinitis was determined by complaints of all four nasal symptoms (sneezing, runny nose, nasal obstruction, and itchy nose/eyes) triggered by aeroallergen exposure with positive SPT and/or sIgE towards aeroallergens.

Asthma was determined by a previous physician's diagnosis or regular use of inhaled bronchodilator or corticosteroid therapy. Patients were considered to have eczema when they fulfilled three of the following criteria: 1. an itchy skin condition, 2. history of a generally dry skin, 3. visible flexural eczema, or 4. a history of atopic disease in a first-degree relative [10].

2.4. Nasal Symptoms

All participants graded the severity of their nasal symptoms from 0 to 100 mm (overall nasal symptoms, sneezing, runny nose, nasal obstruction, and itchy nose) using the Visual Analogue Scale (VAS). Additionally, their quality of life was assessed based on the Sino-Nasal Outcome Test (SNOT-22) questionnaire. 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).

2.5. Radiological Assessment

CT scans paranasal sinus of subjects were retrieved from the institution's Picture Archive Communication System (PACS), de-identified, and reviewed by a radiologist who was blinded to the patient's allergy status. Serial images (1 mm cuts) were assessed by sides on coronal, axial, and sagittal views. The CT PNS images were graded based on the following: 1. centrally limited radiological pattern, 2. anatomical variants of the Ostiomeatal complex, and 3. Lund–Mackay staging system.

The centrally limited disease was graded according to a previous publication, using its figures as reference images [6]. This involved a two-step process. In the first step, each sinus was graded as either centrally limited or diffuse disease. A sinus with normal mucosa or mucosal thickening only of the floor or medial wall (sparing the roof and lateral wall) was graded as a centrally limited disease. A sinus with mucosal thickening involving the roof, lateral wall, all four walls, or completely opacified was graded as a diffuse disease. In the second step, the individual sinus gradings were combined to determine an overall radiological pattern. A patient was defined as having a centrally limited radiological pattern if all sinuses had centrally limited disease. A diffuse radiological pattern was determined if any of the sinuses had diffuse disease.

The anatomical variants assessed include concha bullosa, paradoxical middle turbinate, everted uncinate process, Haller cell, and Agger nasi cell. These were graded as either present or absent. Concha bullosa was documented when there was the presence of air in the middle turbinate. Paradoxical middle turbinate means that the convexity of the middle turbinate is directed laterally. An everted uncinate process is an abnormally projecting uncinate process medially towards the middle turbinate. A Haller cell is an ethmoidal air cell that extends along the medial floor of the orbit. Agger nasi cells are recorded as present when there is an anteriorly located extraluminal air cell that is not confined within the ethmoid bone and is immediately anterior to the insertion of the middle turbinate.

Using Lund–Mackay staging [11], each sinus was scored as either 0 (normal), 1 (partially opacified), or 2 (completely opacified) while the ostiomeatal complex was scored as either 0 (not obstructed) or 2 (obstructed) to give a total score of 12 per side.

2.6. Statistical Analysis

All the collected data from the subjects were analyzed by using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The radiological data were analyzed by sides. The values for continuous variables were produced as means with standard deviation, while the values for categorical data were presented using numbers and percentages. The baseline characteristics between the CRS groups were compared using the Student's *t* test for continuous data, Chi squared for nominal data, and Kendall Tau B test for ordinal data. A *p* value of <0.05 was considered statistically significant.

3. Results

3.1. Participants

A total of 32 CRS patients (68.8% CRS with nasal polyps, age 56.72 ± 13.66) were enrolled in this study. Among these, 15 were allergic CRS and 17 were non-atopic CRS. The baseline characteristics between groups are compared in Table 1. The allergic CRS group was younger, had a family history of atopic diseases, and had documented triggers to aeroallergens. Among those with allergic CRS, 60% had childhood asthma.

The visual analog scale (VAS) for nasal symptoms was higher among the allergic CRS (6.33 ± 2.44 vs. 3.76 ± 2.64, $p < 0.01$). The SNOT-22 total scores were also higher among the allergic CRS group (50.60 ± 21.11 vs. 29.76 ± 23.93, $p < 0.01$).

Table 1. Baseline characteristics comparison between the allergic and non-atopic CRS group.

Factors	**Allergic CRS** ***n*** **= 15**	**Non-Atopic CRS** ***n*** **= 17**	***p*** **Value (95% CI)**
Age (mean ± SD)	50.13 ± 11.95	62.53 ± 12.65	<0.01 (−21.34–−3.48)
Gender (female) (%)	60	23.5	0.04
Smoking %	13.3	11.8	0.89
Family history of atopy (%)	80.0	5.9	<0.01
Trigger (%)			
Mold	73.3	17.6	<0.01
Furry animals	66.7	5.9	<0.01
Dust mites	100.0	58.8	0.01
Childhood asthma %	60.0	-	-
Nasal polyps%	66.7	70.6	0.81
Visual Analogue Scale (VAS)	6.33 ± 2.44	3.76 ± 2.64	<0.01 (−4.41–−0.73)
Total SNOT-22 (mean ± SD)	50.60 ± 21.11	29.76 ± 23.93	0.01 (−37.23–−4.45)

CRS: chronic rhinosinusitis.

3.2. Radiology Scoring between Allergic and Non-Atopic CRS

The centrally limited radiologic pattern was found to be associated with allergic CRS (50% vs. 14.7%, $p < 0.01$). There was no difference in the anatomical variations between allergic and non-atopic CRS patients (Table 2). The Lund–Mackay total score was lower in the allergic CRS group compared to non-atopic CRS (4.97 ± 2.14 vs. 6.59 ± 2.414, $p < 0.01$).

Table 2. Comparison of radiological features between allergic and non-atopic chronic rhinosinusitis.

Radiology Factors	Allergic CRS $n = 30$	Non-Atopic CRS $n = 34$	p Value (95% CI)
Centrally limited sinus disease (%)	50.0	14.7	<0.01
Anatomical Variants			
Concha bullosa (%)	30.0	26.5	0.75
Paradoxical middle turbinate (%)	0.0	5.9	0.18
Everted uncinate process (%)	0.0	5.9	0.18
Haller cell (%)	20.0	8.8	0.20
Agger nasi cell (%)	40.0	61.8	0.08
Lund–Mackay Total sinus score (0–12) (mean ± SD)	4.97 ± 2.141	6.59 ± 2.414	<0.01 (−2.77–−0.48)

CRS: chronic rhinosinusitis.

3.3. Relationship between Anatomical Variation and Central Radiological Pattern

No data were found to support the hypothesis that anatomical variations contribute to the central radiological pattern (Table 3).

Table 3. Radiological Comparison of Anatomical Variants in the Ostiomeatal Complex Between the Central Pattern and Diffuse Disease.

Anatomical Variants	Centrally Limited $n = 20$	Diffuse Disease $n = 44$	p Value
Concha bullosa (%)	35.0	25.0	0.41
Paradoxical middle turbinate (%)	0.0	4.5	0.33
Everted uncinate process (%)	0.0	4.5	0.33
Haller cell (%)	20.0	11.4	0.36
Agger nasi cell (%)	50.0	52.3	0.87

4. Discussion

The centrally limited sinus disease seen in radiology is present in half of the allergic CRS group. Prior studies [5,6,12] reported a lower proportion (20 to 24%) among the atopic CRS group but used standard allergy tests to define allergy without clinical correlation. The difference in patient selection likely explains this discrepancy in the reported proportions. Hence, it is important to integrate clinical symptoms of allergic rhinitis with allergy tests to correctly identify patients with allergic CRS. It is also important to stress that radiology is not the primary tool to diagnose CCAD, as it is poorly sensitive and may even be present in non-atopic individuals. Clinical history and nasal endoscopic findings remain the recommended diagnostic methods. These are then supported by the distinct centrally limited radiological features described here.

Identifying allergic rhinitis among CRS is challenging due to overlapping symptoms. Relying on standard allergy tests, which are the skin prick test (SPT) or serum-specific IgE, is not recommended as positive tests may indicate sensitization that is not clinically relevant. These tests should be correlated clinically with at least two rhinitis symptoms (rhinorrhea, nasal obstruction, nasal itching, and sneezing) triggered by aeroallergen exposure. Allergy is also more likely if the onset of nasal symptoms occurred during childhood to early adulthood. The presence of other allergic comorbidities, such as childhood-onset asthma [13] or eczema, will also support underlying allergy [14]. In this study, underlying allergy among CRS patients was defined as allergic rhinitis identified by the presence of all four nasal symptoms triggered by dust mites, as this is by far the most common aeroallergen at this study location. Additionally, patients must have physician-diagnosed asthma and eczema to increase the likelihood of identifying allergic CRS.

Both CRS and AR patients tend to have a poorer quality of life compared to the normal population [15]. In this current study, the allergic CRS group had a higher disease burden and poorer quality of life compared to the non-atopic group, based on the SNOT-22 and VAS scores. This suggests an increased burden when both diseases are present. Other studies also found high SNOT-22 scores in CRS patients with underlying allergic rhinitis or asthma [16,17]. A study by Laidlaw et al. [18] demonstrated that patients with CRS and comorbid allergies suffered more symptom burden. These patients require additional allergy intervention such as immunotherapy to control their symptoms [19]. This may be accompanied by endoscopic sinus surgery to address the mucosal remodeling over the middle turbinate and restore sinus ventilation. The presence of nasal polyps is not a likely contributor to the higher disease burden among the allergic CRS as this was equally present in both groups. Despite the high symptom burden, these patients are less likely to develop a recurrence of polyps post-surgery compared to other CRS with nasal polyps subtypes (eosinophilic CRS, aspirin-exacerbated respiratory disease, or allergic fungal rhinosinusitis) [20].

The association between anatomical variants and CRS has been inconclusive, with some studies failing to show an association [21–23] while others were able to prove a link [7,24,25]. In this study, anatomical variants of the ostiomeatal complex were not conclusively found to be associated with allergic CRS. Haller cells tended to predominate in the allergic CRS group but this was not statistically significant. This could be due to the low number of patients assessed. In a retrospective review, Sedaghat et al. [7] demonstrated higher odds of developing CRS over four years among allergic rhinitis patients who have Haller cells. The presence of Haller cells is thought to compromise the mucociliary drainage around the already narrowed ostiomeatal opening and this may require further study. Baradaranfar et al. [24] clearly described the association of certain anatomical variants of the sinonasal region with regard to size, location, and amount of mucosal contact to the development and severity of CRS among the patients. Madani et al. also proved that there is a strong correlation between the presence of these anatomical variants and the development of chronic inflammation in the paranasal sinuses [25]. Therefore, the role of anatomical variants in allergic CRS requires further investigation. Additionally, these anatomical variants were not definitively associated with centrally limited radiologic changes when compared to scans showing diffuse disease. A previous study also reported a lack of association between anatomical variants and limited mucosal changes in pansinusitis [26]. This infers that the central radiological pattern is primarily due to underlying allergic mucosal inflammation and is less likely to be due to anatomical variants. Therefore, the treatment aim should include reducing the allergic inflammation with immunotherapy and addressing the consequent mucosal remodeling.

The present study has a few limitations that need to be considered. It recruited a relatively small number of participants, which may not accurately represent allergy in this highly heterogeneous disease. This is due to the strict inclusion criteria for both the allergic and non-atopic groups. The allergic group must have CRS with all comorbid allergic diseases (allergic rhinitis, asthma, and eczema) AND a positive allergy test for aeroallergens. The non-atopic group only included CRS patients without any allergic disease AND negative allergy tests for aeroallergens. CRS patients who did not fit into either group were not recruited and this limited the study population. Prior studies have also shown high allergen sensitization among CRS patients regardless of allergic disease (54–73%), while only a third (26–35%) had allergic rhinitis [27] which explains the limited pool of patients. The size of the anatomical variants was also not considered alongside the bony or mucosal narrowing of the ostiomeatal complex. Other factors that may lead to sinus inflammation, such as mucociliary function and sinus cavity size or variations that may predispose to mucus stasis, were not considered. Another limitation would be that blood eosinophil level was not considered. Serum Eosinophilia is associated with diffuse sinus opacification and may influence this study outcome [28]. However, prior studies have shown that atopy status is closely related to the presence of eosinophilia [29]. Despite

these limitations, this study was still able to reaffirm the association between the central radiological features and allergy.

5. Conclusions

Centrally limited sinus disease is a characteristic of allergic CRS, but this radiological pattern should not be used as the primary diagnostic criterion. It is primarily linked to mucosal disease resulting from allergies and is less likely to be attributed to anatomical variations in the ostiomeatal complex. The potential role of anatomical variations in the ostiomeatal complex in allergic CRS and its radiologic features warrants further investigation.

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