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ORIGINAL ARTICLE

A Case-Control Analysis of Risk Factors Associated With Allergic Fungal Sinusitis Patients

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Abstract

Background: ***Allergic fungal sinusitis (AFS) is a non-invasive sinusitis that typically affects young people.***

Aim and objectives: ***To explain the potential risk factors that may affect patients suffering from nasal polyps with AFS local anatomical variants or general illnesses.***

Methods: ***This case-control study was conducted on 160 patients who were divided into case & control groups. Eighty patients with AFS with nasal polyposis(case group) and 80 cases with nasal polyp without superimposed fungal infection (control group). All participants were evaluated clinically by laboratory investigation (vitamin D level, HbA1c) and radiologically (computed tomography (CT) and chest x-ray) to look for signs of sinusitis, turbinate hypertrophy, nasal septal deviation, conch bullosa, minimal width of infundibulum (MW-I), and maximal length of infundibulum (ML-I).***

Results: ***The mean vitamin D level was considerably lower in the case group (27.86 ±5.92) ng/mL) than in the control group (38.98 ±5.92) ng/mL). The cases had significantly higher anatomical abnormalities (deviated nasal septum and inferior turbinate hypertrophy) than the control group (P value <0.001). MW-I was considerably lower in the case group than in the control group, while it was significantly longer in the case group than in the control group (P value <0.001). Deviated nasal septum, vitamin D, MW-I, and ML-I were significant independent predictors for fungal sinusitis (P value< 0.001).***

Conclusions: ***Features of anatomical abnormalities, such as a notably deviated septum, MW-I, and ML-I, may increase the incidence of fungal sinusitis more than general illnesses such as bronchial asthma and DM. Vitamin D deficiency may play a role in developing superimposed fungal sinusitis.***

Keywords: Allergic fungal sinusitis; Risk factors, vitamin D; computed tomography

1. Introduction

Allergic fungal sinusitis (AFS) is a non-invasive pansinusitis that often affects young people with previous allergic diseases and abnormally high levels of total peripheral eosinophils and immunoglobulin E. [1]

Sociodemographic variables significantly influence the prevalence and incidence of AFS. Patients with chronic sinusitis are at a higher risk of developing AFS. [2]

Although the pathophysiology of AFS remains unknown, one proposed theory is that fungi encountered during normal nasal inhalation are the earliest antigenic stimuli in an atopic host. Eosinophils are involved in a severe inflammatory response after a type I (IgE) and type III (immune complex) mediated reaction.[2] Certain anatomical features, such as deviated septal cartilage or hypertrophied turbinates, might promote the inflammation that blocks the Ostia. When the sinus ostium is blocked, the surrounding conditions are ideal for the growth of the fungus. Allergenic mucin, produced in response to repeated antigen exposures, eventually fills the affected sinuses of an AFS patient. [3]

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AFS is associated with several complications, including proptosis, orbital abscesses, and occasionally vision loss. The illness and surgical intervention put critical neurovascular systems at risk, such as the cranial nerves, dura mater, internal carotid artery, cerebral lobes, and cavernous sinus.[4]

Although nasal polyposis is a hallmark of AFS, the condition is definitively diagnosed once histology is performed post-operatively. Hence, it is crucial to identify the risk factors that might predict the diagnosis of AFS before surgery.[5]

As the risk factors for AFS among patients with nasal polyps have not been adequately quantified, and due to the possibility of illness complication in instances of AFS, this study was designed to clarify the possible risk factors related to patients suffering from nasal polyps with fungal sinusitis locally as anatomical variants (deviated septum, inferior turbinate hypertrophy and concha bullosa) or general illness (DM, Asthma and Vit D insufficiency).

2. Patients and methods

This prospective case-control study was carried out on 160 patients (80 patients with allergic nasal polyposis with fungal sinusitis and 80 cases with nasal polyps without superimposed fungal infection) at the ENT Department from 21 May 2018 to 21 May 2022.

The Institutional Review Board approved the study. Written informed consent was obtained from each participant in the study.

Exclusion criteria were cases younger than 18 years, invasive fungal sinusitis, nasal malignancies, genetic disorders accompanied by ciliary dysfunction, and complex sinusitis due to any reason other than AFS.

Patients were classified as having AFS if they satisfied the primary Bent and Kuhn's criteria for diagnosis (the secondary indicators provide validity to the primary diagnosis) 6.

As outlined in the European position paper on chronic sinusitis, all participants must meet the following requirements 5.: (A) the existence of at least two symptoms; one of these symptoms should be nasal blockage/ obstruction/congestion or nasal discharge (posterior/ anterior/ drip): facial pain/pressure; loss or reduction of smell; duration > 12 weeks (B) either (1) endoscopic evidence of polyps and;-mucopurulent discharge predominantly from the middle meatus and; oedema/ mucosal blockage mainly in the middle meatus (2) and CT alterations: mucosal alterations in the sinuses and ostiomeatal complex.

All of the patients in this study underwent a thorough clinical evaluation (including an ENT examination and an endonasal sinoscopic evaluation), radiological examination (CT of the nose and paranasal sinus, and chest x-ray), and laboratory investigations (vitamin D level, HbA1c).

It was suggested that CT scans be performed in all cases to look for signs of chronic sinusitis(with or without superimposed fungal infection, osteoma, turbinate hypertrophy, and nasal septal deviation.

In addition, several quantitative variables were measured in the coronal view, such as the angle of nasal septum deviation, the maximum length of the infundibulum (ML-I), which was calculated as the longest distance between the infundibular ostium and the highest point of the uncinate process (semilunar hiatus), and the minimum infundibulum width (MW-I), which was estimated as the shortest distance between the infundibular walls 7.

The vitamin D concentration in the blood was determined using an enzyme-linked immunosorbent assay (ELISA) for human vitamin D immunoassay (Calbiotech, Inc., Spring Valley, CA). The same investigator performed All of the measurements using the same equipment in a controlled environment. The blood was centrifuged at 1250g for 15 minutes.

Statistical analysis

SPSS v27 (IBM Corp., Armonk, New York, USA) was used for the statistical analysis. Histograms and the Shapiro-Wilks test were employed to determine whether or not the data had a normal distribution. Mean and standard deviation were used to depict quantitative parametric data (SD). Frequency and percentage were used for qualitative variables. The unpaired student t-test was used to evaluate the parametric data for the quantitative variables. In contrast, the Chi-square test or Fisher's exact test was used for the qualitative variables. A two-tailed P value < 0.05 was statistically significant.

3. Results

Demographic data and medical history were insignificantly different between both groups Table 1.

Table 1. Demographic data and medical history of the studied groups

		Case group (n=80)	Control group (n=80)	P value	Mean difference / Odds ratio (95%CI)
Age (years)		29.14 ± 9.38	32.51 ± 13.25	0.065	-3.38(-6.96:0.21)
Sex	Male	36 (45%)	29 (36.25%)	0.26	1.44(0.76:2.71)
	Female	44 (55%)	51 (63.75%)		
Medical history	DM	7 (8.75%)	1 (1.25%)	0.063	7.58(0.91:63.07)
	Smoking	20 (25%)	26 (32.5%)	0.295	0.69(0.35:1.38)
	Asthma	29 (36.25%)	20 (25%)	0.123	1.71(0.86:3.37)

*: Significant as P value ≤ 0.05, Data are presented as mean ± SD or frequency (%), DM: Diabetes mellitus.

Vitamin D levels in the case group were 27.86 (±8.46) ng/mL, whereas levels in the control group were 38.98 (±5.92) ng/mL. The case group had considerably lower vitamin D levels compared to the control group (P <0.001). Fig. 1

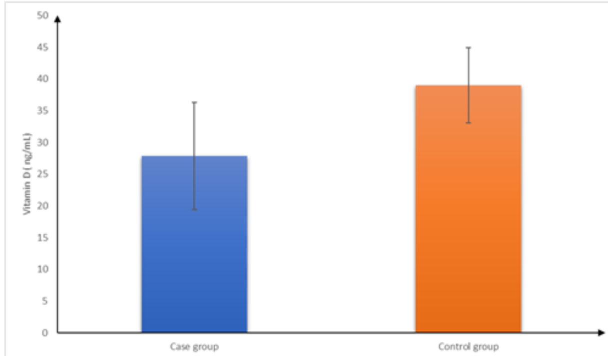

Figure 1. Vitamin D of the studied patients

The prevalence of deviated nasal septum and inferior turbinate hypertrophy was markedly more prevalent in the case group than in the control group (P value <0.001). The prevalence of concha bullosa was insignificantly different between both groups. Table 2

Table 2. Anatomical variants of the studied groups

	Case group (n=80)	*Control group (n=80)*	*P value*	*Odds ratio (95%CI)*
Deviated nasal septum	51 (63.75%)	14 (17.5%)	<0.001*	8.29(3.97:17.29)
Inferior turbinate hypertrophy	49 (61.25%)	23 (28.75%)	<0.001*	3.92(2.02:7.59)
Concha bullosa	8 (10%)	3 (3.75%)	0.118	2.85(0.73:11.17)

*: Significant as P value ≤ 0.05, Data are presented as frequency (%).

The case group had a significantly lower MW-I and significantly higher ML-1 than the control group (P value <0.001). The angle of NSD was insignificantly changed between the case and the control groups. Table 3

Table 3: MW-I and ML-I of the studied groups

	CASE GROUP (N=80)	CONTROL GROUP (N=80)	P VALUE
MW-I (MM)	3.07 ± 0.81	4.34 ± 1.38	<0.001*
ML-I (MM)	9.69 ± 1.71	8.02 ± 2.03	<0.001*
ANGLE OF NSD	-0.26 ± 8.55	-1.99 ± 7.89	0.185

*: Significant as P value ≤ 0.05, Data are presented as mean ± SD, MW-I: Minimal width of infundibulum; ML-I: Maximal length of infundibulum, NSD: Nasal septal deviation.

Deviated nasal septum, vitamin D, MW-I, and ML-I were significant independent predictors for fungal sinusitis (P value=0.001, <0.001, 0.002, and 0.001, respectively), while inferior turbinate hypertrophy was not. Table 4

Table 4: Multivariate regression analysis for prediction occurrence of fungal sinusitis

	COEFFICIENT	ODDS RATIO	95% CI	P VALUE
DEVIATED NASAL SEPTUM	1.810	6.114	2.054 - 18.196	0.001*
INFERIOR TURBINATE HYPERTROPHY	0.556	1.744	0.603 - 5.042	0.304
VITAMIN D (NG/ML)	-0.182	0.833	0.772 - 0.899	<0.001*
MW-I (MM)	-0.955	0.386	0.235 - 0.636	0.002*
ML-I (MM)	0.464	1.591	1.190 - 2.128	0.001*

*: Significant as P value ≤ 0.05, CI: Confidence interval, DM: Diabetes mellitus, MW-I: Minimal width of infundibulum; ML-I: Maximal length of the infundibulum.

4. Discussion

According to EPOS 2020, the presence of two or more symptoms, including but not limited to nasal obstruction/ blockage/ congestion or nasal discharge (posterior/anterior nasal drip) with or without facial pain/pressure, reduction or loss of smell, for 12 weeks identifies people as having chronic rhinosinusitis with or without nasal polyps 8. AFS has been recognized as one of the most common forms of chronic rhinosinusitis (CRS), distinguished by a type I hypersensitivity to fungi and eosinophilic mucus containing non-invasive fungal hyphae inside the sinuses. [9]

Due to the low incidence of AFS, the previously indicated general risk factors cannot account for all its causes.[9] Our study considered anatomical variants such as the deviated nasal septum, inferior turbinate hypertrophy, and concha bullosa of middle turbinate or general illnesses such as diabetes, bronchial asthma, or low vitamin D.Fig.2

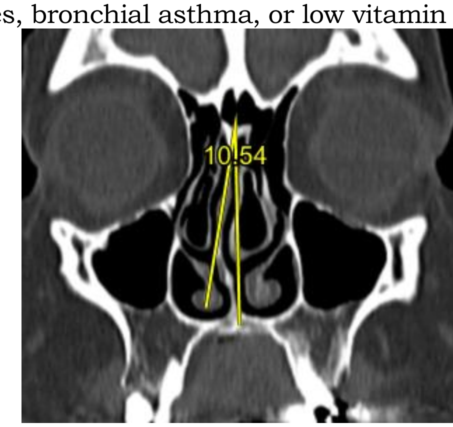

Figure 2. Deviated nasal septum to the right side for about 10 degree associated with bilateral

concha bullosa prominent at the left side.

Our results showed that the cases group had a significantly decreased vitamin D level compared to the control group. CT scans revealed a greater prevalence of nasal anatomical changes; the case group had substantially higher deviated nasal septum and Inferior turbinate hypertrophy than the control group. The case group had markedly lower MW-I with significantly longer ML-I than the control group. Deviated nasal septum, vitamin D, MW-I, and ML-I were significant independent predictors for AFS. Fig. 3

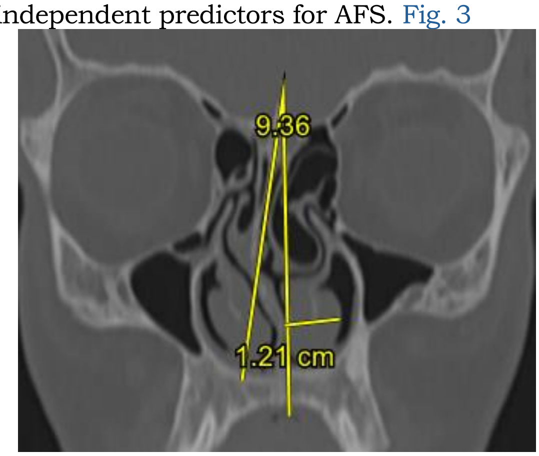

Figure 3. Deviated nasal septum to the left side for about 9 degree associated with left concha bullosa and bilateral hypertrophied inferior nasal turbinates about 12 mm. thickness at the left side causing nasal narrowing.

Supporting our results, Rehman et al. [10] reported that nasal septum deviation and turbinate hypertrophy had no significant relationship as a risk factor for AFS.

DM alters the humoral and cellular responses of both the innate and adaptive immune systems. Major histocompatibility complex class I expression is downregulated. Changes are made to the complement's structure and the proportion of activation to restriction. Hyperglycemia, polymorphonuclear cell generation, neutrophil migration, chemotaxis, and phagocytic activity are all suppressed in poorly managed diabetes.[11]

In addition, endothelial cell injury, fungal invasion, germination, and fast filamentous development of mucormycosis are all produced by the overexpression of the glucose-induced glucose-regulated protein (GRP) that occurs during diabetic ketoacidosis. [12]

Additionally, Fernadez et al.[11] showed that poorly managed diabetes was a general risk factor for fungal sinusitis.

In this regard, Nynut et al.[14] identified a correlation between the rising rates of diabetes and AFS among diabetic individuals. They also reported that plasma glucose level, HbA1C, and duration of diabetes were insignificant predictors of fungal sinusitis.

Moreover, Jiang et al.[15] demonstrated sinus fungus patients had a higher prevalence of diabetes.

In addition, a vitamin D deficit is associated with atopic disorders, including asthma, allergic rhinitis, and anaphylaxis, which negatively impact the musculoskeletal system. [16]

Vitamin D insufficiency is associated with decreased production and secretion of interleukin-4 (IL-4) and IL-10, two of the most essential cytokines in type 2 immune response responsible for interferon-gamma production, the most crucial cytokine in type 1 immune response 17. Vitamin D deficiency also requires greater glucocorticoid dosages to produce therapeutic benefits, suggesting that vitamin D may contribute to glucocorticoid actions in cells 18. Hence, vitamin D insufficiency has been linked to a compromised immune system, which may play a role in the pathogenesis of rhinosinusitis .[16] Fig. 4

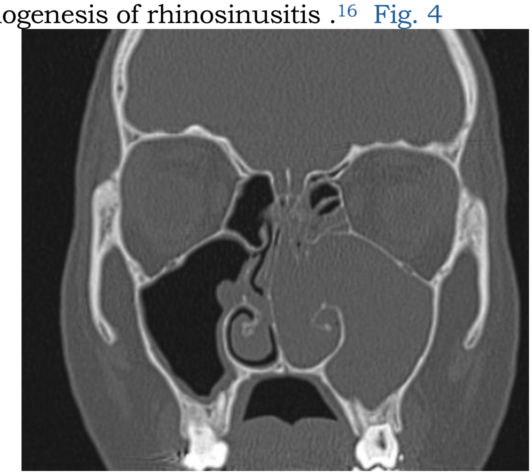

Figure 4: coronal bone window scan shows left antro-choanal polyp extends to the nasal cavity with right side deviated nasal septum and obliterated osteomeatal complex.

Zand et al. [13] found that there was a substantial adverse connection between the Sino-nasal Outcome Test (SNOT-22) and vitamin D blood levels. A study by Wang et al.[16] found that vitamin D concentration was significantly reduced in chronic rhinosinusitis patients with nasal polyps. As a result, measuring patients' vitamin D levels as part of their standard care might provide helpful information for assessing the extent of their CRs.[16]

Fernadez et al., 11 showed a greater incidence of anatomic nasal alterations observed at CT scans in fungal sinusitis cases. The primary anatomic modification substantially related to fungal sinusitis was an anterior septum deviation producing nasal or sinus obstruction, the most prevalent of the nasal abnormalities studied. fig. 5

The abnormality in the front of the septum can cause or amplify airflow turbulence, which might aid in the deposition of fungal spores, 13. Finally, Nasal obstruction contributes to poor airflow, which causes inflammation and changes in mucociliary clearance.[10] The link between the infection site and the anatomic change site in all of the cases in our study supports this concept and the unilateral beginning of AFS.[13]

It was established that the anatomical variables influence the maxillary sinus (MS) mucosal thickenings, and the MW-I and ML-I were the foremost risk variables in sinusitis,. [7]

In addition, Shin et al.,[11] and Alkire et al.,[12] found that fungal sinusitis patients had a significantly lower mean MW-I and more extended ML-Ithan control.

Sinus drainage is blocked by the sinus ostium, which can be exacerbated by anatomical factors such as turbinate hypertrophy or septal deviation. As a result, the paranasal sinuses become a favourable environment for fungus,. [13]

The nasal cavity filters out larger particles like airborne fungus spores and humidifies and warms the incoming air during inspiration.[14] The mechanics of nasal fluid flow are unclear; however, research has shown that most airflow and turbulence occur in the small space between the nasal septum and middle turbinate during everyday inspiration.[10, 14, 15] Therefore, this spot might be the first to collect fungus spores.

This concept might explain the presence of middle turbinates at the start of the AFS course. In addition, some anatomical defects, such as anterior septum deviation, may generate or exacerbate airflow turbulence, favouring the deposition of fungal spores 15, 16. Finally, the resulting nasal blockage results in reduced ventilation, inflammation, and a change in mucociliary clearance. [12, 17]

Our study had some limitations; it was a single-centre study with a modest sample size; thus, the results may differ elsewhere. Further studies with larger sample sizes are recommended to ensure the significant risk factors affecting AFS. The treatment of vitamin D deficiency may offer possible management for AFS.

5. *Conclusion*

Anatomical variations such as marked septal deviation and concha bullosa may increase the incidence of AFS more than general illness, as bronchial asthma and diabetes mellitus may be due to improper drainage in local causes. Vitamin D deficiency may have a role in developing superimposed AFS.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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