**Original Research Article**

**Inflammatory characterization of different non-allergic rhinitis in patients attending tertiary care hospital**

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**ABSTRACT**

**Background:** Non-allergic rhinitis is a chronic inflammation of nasal cavity, which can be classified based on the level of eosinophil. Thus, the present study aimed to characterize the various types of non-allergic rhinitis.

**Methods:** This study conducted during the period of 1 year from April 2019 to February 2020 in the ENT department of MNR Medical College and Hospital, Sangareddy. A total of 60 participants were enrolled in this study.

**Results:** In case of non-allergic rhinitis, the nasal IL-17 level was 27.31±5.1, IL-4 level was 44.24±21.31, as well as serum IL-4 and IL-17 level was 50.1 and 31.06 respectively. The control group IL-4 and IL-17 level were respectively less (p<0.05). But the IL-10 level (3.7) and proportion of tregs in peripheral blood (5.2) were lower than the control group (p<0.05). There was no significant difference found between the non-allergic rhinitis group and allergic rhinitis group or the non-allergic rhinitis without eosinophilia group and the control group (p>0.05).

**Conclusions:** Hence, the non-allergic rhinitis was classified on the basis of eosinophil level, allergic rhinitis and NARES had similar kind of inflammatory response, but two different types of non-allergic rhinitis had different inflammatory characteristics. Therefore, it is recommended to classify the rhinitis on the basis of eosinophil level.

**Keywords:** Allergic rhinitis, Eosinophil level, Non-allergic rhinitis

**INTRODUCTION**

Rhinitis is one type of chronic inflammation of nasal mucosa. Rhinitis is classified as allergic rhinitis (AR) and non-allergic rhinitis (NAR). There were several studies done on allergic rhinitis around the globe.¹,² They reported factors involved in AR were eosinophilia and hyperactive eosinophil. The pathogenesis of AR mainly depends on the regulation of Th1, Th2, Th17 and regulatory T cell (Tregs). Although there were several questions arise regarding non-allergic rhinitis. Around 14% of rhinitis involved non-allergic rhinitis with eosinophilia syndrome, a chronic inflammation of nasal mucosa.³ The clinical symptoms such as, nasal itching, obstruction, rhinorrhea and sneezing were similar in case of NARES as well as in AR. There is large volume of eosinophilia in nasal secretions of NARES patients without any systemic manifestations. However, there was no clear data available regarding pathogenesis of NARES. Few data showed that NARES may be due to nasal IgE level.⁴,⁵ The NARES also related to nasal polyps, aspirin intolerance, bronchial asthma etc.⁶-⁸ But the mechanism of NARES pathogenesis has not been cleared yet. Wang et al study revealed that NARES patients have symptoms like nasal, systemic eosinophilia and lower airway inflammation, and pathogenesis are similar to AR.⁹ The hyper activation of Th2 cells leads to eosinophilic inflammation.¹⁰

Therefore, the present study focused on NAR with eosinophilic and NAR without eosinophil group, compared both the groups with control group.
METHODS

This study was conducted during the period of 1 year from April 2019 to February 2020 in the ENT Department of MNR Medical college and Hospital, Sangareddy, Telangana, India. The total numbers of participants were 60 in this study. The systemic disease, deviation of nasal septum, nasosinusitis, nasal polyps etc., are included in the exclusion criteria. NAR and AR were classified according to the study done by Wallace et al.11 The clinical findings of all patients were recorded, performed SPT, blood examinations and nasal lavage for rhinitis patients. The prick test was done and reading was recorded after 15 minutes. The test result considered positive if pale yellow skin papule surrounding erythema. Nasal douche test was performed with 10 ml of warm 0.9% normal saline was injected i.n. This procedure repeated 3 times and collected the fluid with funnel. Later 5 ml of fluid used for testing. 20 µl of sediment part was used for smear preparation. The total number of inflammatory cells were counted under 200 HP microscope. Enzyme linked immunosorbent assay was performed to calculate the value of IL-4, IL-17, IL-10, and IFN-ɤ according to the manufacturer’s protocol (Elabscience Biotechnology Co. Ltd, MD, USA). The ratio of CD4+ CD25+ FOXP3+Treg/CD4+T was diagnosed by using Becton, Dickinson and Company, NJ, USA).

Statistical analysis

All the data were statistically analyzed by statistical software SPSS 20.0.

RESULTS

A total of 60 participants were included in this study. Among all 16 patients with NARES (age- 35.55±13.51, male: female- 9:7), 12 patients with NAR without eosinophilia (age- 37.43±14.1, male: female- 6:6), 16 patients with AR (age- 36.43±13.63, male: female- 10:6), and 16 healthy individuals (age- 37.53±12.3, male: female- 8:8) (Table 1).

| Group                      | Patient number | Age          | Male: Female ratio | Significant value |
|----------------------------|----------------|--------------|--------------------|-------------------|
| NARES                      | 16             | 35.55±13.51  | 9:7                | P<0.05            |
| NAR without eosinophilia   | 12             | 37.43±14.1   | 6:6                | P<0.05            |
| AR                         | 16             | 36.43±13.63  | 10:6               | P<0.05            |
| Control                    | 16             | 37.53±12.3   | 8:8                | P<0.05            |
| Total                      | 60             | -            | 33:27              |                   |

Table 1: Socio-demographic data of total 60 participants.

Table 2: Comparison of different cytokine levels in each group.

| Group                      | Nasal IL-4     | Nasal IFN-ɤ | Nasal IL-4 | Nasal IL-10 | Serum IL-4 | Serum IFN-ɤ | Serum IL-17 | Serum IL-10 | Significant value |
|----------------------------|----------------|-------------|------------|-------------|------------|-------------|-------------|-------------|------------------|
| NARES                      | 44.24±21.31    | 29.89       | 27.31±5.1  | 3.7         | 50.1       | 357.93      | 32.05       | 3.74        | P<0.05           |
| NAR without eosinophilia   | 25.54          | 7.62        | 19.64      | 5.32        | 32.13      | 495.03      | 20.1        | 3.95        |                  |
| AR                         | 40.35          | 12.15       | 26.35      | 4.84        | 34.73      | 364.33      | 31.23       | 4.23        |                  |
| Control                    | 26.92          | 9.31        | 17.92      | 5.01        | 21.92      | 376.04      | 23.86       | 4.13        |                  |

In case of non-allergic rhinitis, the nasal IL-17 level was 27.31±5.1, IL-4 level was 44.24±21.31, as well as serum IL-4 and IL-17 level was 50.1 and 31.06 respectively. The control group IL-4 and IL-17 level were respectively less (p<0.05). But the IL-10 level (3.7) and proportion of tregs in peripheral blood (5.2) were lower than the control group (p<0.05). There was no significant difference found between the non-allergic rhinitis group and allergic rhinitis group or the non-allergic rhinitis without eosinophilia group and the control group (p>0.05). The expression of IFN-ɤ in the nasal lavage fluid was higher in the NARES group than NAR without eosinophilia. However, the expression of IFN-ɤ showed no significant difference among 4 groups (p>0.05) (Table 2).

DISCUSSION

As per the previous study report, the pathogenesis of AR depends on the regulation of Th1/Th2 cells and Treg/Th17 cells. The cellular immune mechanism rely on Th1 cells, because it releases IFN-ɤ and TNF-β. In case of patients with AR or asthma, increase the
differentiation of Th0 cells into Th2 cells, which makes Th2 cells predominant. Th2 cells primarily responsible for IL-4, IL-5 and IL-3 and regulate the humoral immunity. The production of IgE regulated by IL-4, IL-3 and IL-5 mediates eosinophil differentiation and migration. IL-17 released by Th17 cells which promotes inflammation and recruits’ neutrophils. The effector T cells function inhibits by Tregs through release of immune suppressor IL-10 and TGF-β. The hyper activation of Th2 cells leads to eosinophilic inflammation. 10 In this present study reported nasal and serum IL-4 and IL-17 levels increased and Tregs were decreased in NARES and AR patients. Also, activation of Th2 and Th17 was found in two groups and Tregs suppressive function was inhibited. There were no significant differences found in expression of cytokines level in NAR without eosinophilia control group. The IFN-γ levels were increased in NARES group and AR group. The serum IL-10 levels were decreased in NARES and AR group, but there was no statistically significant found may be due to small sample size. The study done by Powe et al reported nasal IgE level was increased in NAR and AR group.5,5 The phenomenon called “entopy” deals with local IgE elevation, which can induce the nasal allergic response in NAR patients without systemic inflammation. Therefore, the concept of local allergic rhinitis was introduced and it’s related to patients with nasal Th2 inflammation, without systemic allergic reactions. 47%-62.5% NAR patients have local allergic reactions.5,14 In this present study NAR group was divided in two such as, NARES and NAR without eosinophilia groups. As compared with the control group, NARES group exhibited systemic Th2 and Th17 responses, which similar to the AR group. Therefore, NARES is the local as well as systemic nasal disease. However, there is no strong data which can prove the role of eosinophilia in the pathogenesis of LAR, as well as association between LAR and NARES group. It has been reported that NARES is associated with bronchial asthma, aspirin intolerance and nasal polyps.6,8 All these reports suggest that NAR is the risk factor for bronchitis and asthma.5,16 The pathogenesis of asthma is regulated by Th17, Th2 and reduced suppressive function of Tregs. The present study showed that NARES patients reported nasal and systemic inflammation mediated by Th2 and Th17 cells, Tregs numbers decreased and airway inflammation associated with asthma, which proved that NARES was risk factor for lower airway disease. In this study NARES patients showed nasal, lower airway and systemic eosinophilic inflammation which similar to AR.9

CONCLUSION

In conclusion, rhinitis is divided as NAR and AR based on “atopy”. Amin et al. reported asthma into atopic and nonatopic asthma, which based on eosinophilic infiltration. Previously it is characterized by Th2 cell dependent airway inflammation and increased eosinophil level, IL-4+ cells, IL-5+ cells and mast cells, later it is defined as non-Th2 cell induced airway inflammation.17,18 Therefore, it is recommended that classify the rhinitis based on eosinophilic infiltration. But the large number of samples required to standardize the phenomenon. Also, various degree of rhinitis and steroid sensitivity in NARES and AR will require further elaborated research.

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