

# Salicylate Food Intolerance and Aspirin Hypersensitivity in Nasal Polyposis

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## ABSTRACT

**Background:** A clear association between allergy and nasal polyposis (NP) is not determined and the role of food intolerance in patients with NP is not investigated by oral food challenge (OFC). **Objective:** To investigate the relation of salicylate food intolerance and atopy in patients with NP according to recurrence and aspirin sensitivity. **Methods:** A cross sectional multicenter study was done in two tertiary centers for allergy in Iran. Adult patients with NP were selected for the study that had been referred to allergy clinics. The oral aspirin challenge (OAC) test was performed to identify aspirin exacerbated respiratory disease (AERD) and the OFC test was used to investigate food intolerance. Atopic evaluation was performed by skin-prick tests, nasal smear and blood eosinophil count as well as serum total IgE. **Results:** One hundred and nineteen Iranian patients (female to male ratio 1.05) with NP were enrolled (mean age,  $38 \pm 11$  years). Recurrence of nasal polyposis was 64.7%. OAC was performed in all cases; 43.79% cases had aspirin hypersensitivity. In addition, OFC tests determined that 69.9% of patients had salicylate food allergy. Salicylate food intolerance was significantly higher in NP cases with AERD than in aspirin tolerant patients ( $p < 0.05$ ). Yet, positive skin prick test was not associated with NP recurrence and AERD. **Conclusion:** Atopy and NSAID exacerbated respiratory disease; therefore, they can both be considered as predictors of NP recurrence. Our study also showed that salicylate food intolerance was associated with AERD in nasal polyposis.

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**Keywords: Nasal polyposis, Food allergy, Aspirin hypersensitivity, Recurrence, Salicylate**

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## INTRODUCTION

Nasal Polyposis (NP) is a chronic inflammatory condition in nasal and para-nasal cavities; it is mostly characterized by eosinophil infiltration (1,2). A multifactorial etiology has been considered to explain its pathophysiology (2). Among cases in this study, the role of allergy remains unclear (3).

“Samter’s triad,” is a set of conditions that includes chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma and aspirin hypersensitivity; it is also called aspirin-exacerbated respiratory disease (AERD) or NSAID exacerbated respiratory disease (NERD). Research has shown that about 8-26% of patients with NP also had AERD, and this was found to be more prevalent in Iran (4-6). This triad of conditions can also reinforce the correlation between allergy and NP.

Recurrence of nasal polyposis has been reported in 20-60% of patients but factors that indicate predisposition to the condition remain obscure (7,8). Considering the pathogenesis of nasal polyposis recurrence, a possible and even strong correlation can be suggested for allergy and recurrent NP. Previous studies have identified the role of eosinophil and Matrix metalloproteinase 9 (MMP 9) in both recurrence of nasal polyposis and pathophysiology of allergy (9-12).

Food allergy is a subgroup of reactions related to immunologic based hypersensitivity, which leads to respiratory, gastrointestinal and dermal hypersensitivity reactions. Salicylate intolerance is also a subgroup of nonspecific pseudo allergy hypersensitivities triggered by exposure to silicylic acid and its derivatives, which can be found in some fruits, vegetables and spices (13,14).

To date, no study has been done to evaluate salicylate food intolerance in NP patients and data on the association of atopy and NP recurrence is limited. Therefore, this study was done to assess the association of salicylate food intolerance and NP and to investigate the association of atopy and recurrent NP.

## MATERIALS AND METHODS

This cross sectional study was done on patients referred to Allergy clinics of Rasool-e-Akram Hospital, Tehran, Iran as well as Emam Reza Tertiary Center, Shiraz, Iran from 2012 to 2016. Sixty patients from each center were enrolled for participation in the study.

**Eligibility Criteria.** Patients diagnosed with chronic rhino sinusitis with nasal polyposis (CRSwNP) were included in this study. CRSwNP diagnosis was based on the European position paper on rhino sinusitis and nasal polyps (EPOS 2012) (15). Cases of pregnancy or gastropathy such as peptic ulcer disease or coagulopathy or a history of anaphylactic shock reaction to NSAID were excluded from the survey.

**Data Gathering.** Records were made for demographic and clinical findings in previously prepared data sheets of patients with a history of nasal polyp surgery and numbers of procedures. Complete allergy tests were done on patients including skin-prick tests for the most commonly inhaled allergens.

Presence of AERD was investigated in patients by selecting cases that had taken the oral aspirin challenge (OAC) test by a single blinded 2-day study. Force expiratory volume in one second (FEV1) was measured before the study and patients with a FEV1 score of at least 70% were entered for the study. Aspirin was administered in doses of 20, 40, 80, 160, and 320 mg every 90 minutes until the cumulative dosage reached to 500 mg. A

positive reaction was defined as a decline in FEV1 of at least 15% combined with a naso-ocular reaction, pure lower respiratory tract reactions (related symptoms with 20% decline in FEV1) or naso-ocular reactions only (6).

The oral food challenge (OFC) provides an accurate diagnosis of immediate and delayed reaction to food; it is detailed in, Nowak-Wegrzyn et al. and employed to identify the presence of allergic reaction to salicylate in food (16). Food samples were selected from the most common foods in the Iranian diet that contain salicylate; mushroom, green pepper, olive, tomato, spinach, drill, cucumber, broccoli, green apple, raze, cherry, red grape, sago, almond, peanut, cinnamon, thyme, mustard, curry powder. The number of foods used in OFC tests was determined by each patient's allergy history. Use of anti histamine or anti leukotriene drugs was discontinued 5-7 days before an OFC test and at least one week after an OAC test. According to each patient's allergy history, a 0.5-gram amount of each selected food was administered. The dose was then doubled at 30-minute intervals (0.5 grams, 1, 2 grams, 4 grams, 8 grams, 16 grams, 32 grams) until the cumulative dose of 100 gram was achieved. Each patient was observed for one hour in the clinic for early IgE mediated clinical allergy presentation. Telephone calls and visit were also made 24 hours later in order to assess for late allergy manifestation. Any respiratory, gastrointestinal, or mucocutaneous reaction was considered a positive OFC result. On reaching this point, the challenge was stopped and symptoms were relieved by medical treatment.

**Statistical Analysis.** Data were recorded and entered into SPSS 15. Descriptive analysis was used to estimate the mean age of the patients as well as to determine prevalence of allergy in patients with nasal polyposis. Then the chi-square test was applied in order to compare occurrences of these disorders between the 2 groups of patients; the group with recurrent NP and that with non-recurrence. The significant p-value in all these comparisons was considered  $<0.05$ .

**Ethical Issue.** The study was approved by the ethical committee of Tehran as well as Shiraz University of Medical Science. Informed consent was granted for the entire protocol and forms were compatible with the Helsinki Declaration were obtained from each patient. Ultimately, those who agreed to enroll were recruited for participation in the study.

## RESULTS

A total of 119 patients (60 from each center) with CRSwNP were enrolled in the study (51.3% female and 48.7% male patients) with a mean age of  $38 \pm 11$  years.

Of 119 patients, 77 (64.7%) had a history of nasal polypectomy that was considered recurrent nasal polyposis. Among these, 53 patients (44.5%) had experienced one episode of polypectomy and 24 (20.2%) had experienced two or more episodes of polyp surgery. The mean age of patients with recurrent NP was  $38 \pm 11$  years. The female to male ratio was 1.08 in recurrent NP.

Furthermore, allergy evaluation markers were identified in NP cases. 71 patients (59%, CI95%: 50.66 - 68.57) had IgE serum level of more than 100 IU/ml. In addition, 62 patients (52.1%) had positive prick test results. Among the allergens used in prick tests, patients most commonly showed sensitivity to Ray grass (27.4%, CI95%: 19.12 - 35.75). Values showing prevalence of sensitivity to other allergens are provided in supplementary files.

A serum eosinophil count of more than 450 was confirmed in 22 patients (18.4%, CI95%: 11.44 – 25.53), and the nasal smear eosinophil proportion > 10% was detected in 21 patients (17.6%, CI95%: 10.73 – 24.57). Aspirin challenge test was done on 119 patients and sensitivity was determined in 52 (43.79%). Oral food challenge test, which could be done on 73 cases, was also positive in 51 patients (69.9%, CI95%: 59.16 – 80.57). Among the salicylate food used in OFC, patients had the most sensitivity to green pepper (49.3%, 36 out of 73, CI95%: 37.65 – 60.98). Values for prevalence for other foods are provided in supplementary files.

Additionally, the mentioned allergy markers and test results were compared between cases with recurrent versus non-recurrent nasal polyposis and are presented in Table 1.

**Table 1. The comparison of allergy markers between recurrent and non-recurrent nasal polyposis.**

Allergy Test	Recurrent NP%(no/total.no)[CI95%]	Non-recurrent NP%(no/total.no) [CI95%]	P Value
IgE level >100	70.2%(52/74)[59.68-80.86]	51.3%(19/37)[34.69-68.02]	0.041
Positive Prick test	57.1%(44/77)[45.91-68.38]	45.0%(18/40)[29.09-60.91]	0.146
Serum Eosinophil >450	23.6%(18/76)[13.97-33.40]	9.7%(4/41)[0.39-19.12]	0.052
Nasal Eosinophil >10%	25.0%(19/76)[15.11-34.89]	4.8%(2/41)[0-11.68]	0.005
Positive OAC*	53.2%(41/77)[41.92-64.57]	26.1%(31/42)[60.11-87.51]	0.004
Positive OFC**	75.0%(39/52)[62.94-87.06]	57.1%(12/21)[34.62-79.67]	0.112

\* Oral Aspirin Challenge

\*\* Oral Food Challenge

Also, they were compared between cases with one versus two or more episodes of recurrence (Table 2).

**Table 2. The comparison of allergy markers between one episode versus two or more episodes of nasal polyposis recurrence.**

Allergic Test	One time recurrence of NP%(no/total no)[ 95CI]	Two times or more recurrence of NP%(no/total no) [95CI]	P Value
IgE level>100	66% (33/50) [52.54_79.46]	79.17% (19/24)[62.02_96.32]	0.188
Positive Prick test	54.72% (29/53) [41_68.44]	62.50% (15/24)[42.06_82.94]	0.35
Serum Eosinophil>450	25.00% (13/52)[12.94_37.06]	20.83% (5/24)[3.68_37.98]	0.465
Nasal Eosinophil>10%	26.92% (14/52)[14.57_39.27]	20.83% (5/24) [3.68_37.98]	0.395
Positive ACT	50.94% (27/53)[37.16_64.72]	58.33% (14/24)[37.52_79.15]	0.362
Positive OFC	71.43% (25/35)[55.91_86.95]	82.35% (14/17)[62.75_100]	0.311

\* Oral Aspirin Challenge

\*\* Oral Food Challenge

Besides, comparison of results of the oral food challenge with foods containing salicylate between sensitive to aspirin (AERD) cases and non-sensitive ones (non-AERD) resulted in p-value <0.05 (0.019). In more detail, 29 patients out of 35 (82.8%, CI95%: 69.91 – 95.80)

AERD cases had salicylate food allergy; however, 22 patients out of 38 (57.8%, CI95%: 41.67 – 74.12) non-AERD cases had positive results for oral food challenge. Yet, comparisons of each food's hypersensitivity between these two groups resulted in non-significant p-values (>0.05).

## DISCUSSION

Nasal Polyposis (NP) is a chronic inflammatory disease of the upper airway. The mean age of patients in the study was about 38 years old with a female to male ratio of 1.05. Moreover, estimating the mean age of recurrent NP cases was also shown to be similar to the mean age of overall NP cases. The female to male ratio was also near the mentioned result for overall NP patients (1.08). Previous studies have not determined any difference in age and sex ratio of recurrent NP compared to overall NP cases (17,18).

According to these common findings in pathophysiology of allergy and NP, results show a high occurrence of allergy in cases of nasal polyposis (11, 12). In addition, another issue in NP is its recurrence. The study by Lou et al. demonstrated that tissue eosinophil absolute count >55 or tissue eosinophil proportion >27% total cell can be considered as a predictor of recurrence in NP (9). In addition, research has highlighted the effect of aspirin desensitization; accordingly, its anti-inflammatory effect may reduce symptoms and medication score in NP (19). Therefore, it seems logical that there is a greater probability of allergy occurrence in recurrent NP compared to non-recurrent cases. For assessment of these hypotheses, the allergy indicators were measured in NP cases and then comparisons were made between recurrent NP and non-recurrent cases.

More than half of the patients (64%) were found to have IgE serum levels more than 100 IU/ml. This finding is compatible with the research reported in Small et al. study, in which serum IgE levels were higher than normal values in 18 out of 24 patients that had previously experienced polypectomy and had recurrence of NP (20). Research also determined that cases of recurrent NP had higher levels of serum IgE compared to non-recurrent cases. However, this difference was not shown between one episode and other episodes of recurrent NP. No similar study has been done to date to assess this hypothesis.

Furthermore, about half of the patients (53%) had positive prick test results with dominance of Ray grass. Sin et al. also found that about 66.3% of 95 patients with nasal polyposis had positive results for skin prick tests (21). This showed no significant difference between recurrent NP and non-recurrent cases.

Serum eosinophil higher than 450 and nasal smear eosinophil higher than 10 % was also found in 18.8% and 17.9% of patients in this study, respectively. These results are almost far from the estimated rate of elevated blood eosinophil in the study of Anton *et al.* which reports about 63% (29/46) (22). This variation may relate to the low number of cases involved in Anton's study as well as specific environmental factors, such as local air-borne allergens in Iran. Also, assessing the rate of this allergy marker in cases of recurrent NP showed that it was significantly higher in patients with recurrent NP with no significant difference in the rate by further recurrence. Again, no other similar study can be found in relation to this issue.

In addition, for estimating the prevalence of AERD in NP, aspirin hypersensitivity was tested using the aspirin challenge test and results were positive in 43.79% of the

patients. This result is compatible with that reported in Nabavi *et al.* on a study in Tehran, Iran, that reported about 48.8% (39 out of 80 patients) (6). However, previous studies declared that the rate of AERD among NP patients was about 8-26% (4). These differences in the formerly mentioned studies can be attributed to the genetic basis of AERD and racial difference between patients (23,24). Moreover, this item was also significantly higher in recurrent cases of NP. However, the number of recurrence indicated no difference in prevalence of the positive results of this item. Again, no previous survey has yet been done to assess this hypothesis.

Salicylate food allergy was also determined by taking consideration of a patient's history and by conducting the oral food challenge test to determine if it had higher rate of prevalence among NP patients. About 69.9% of cases were shown to have sensitivity to salicylate-containing foods. Green pepper and red grape were the two most common foods by which patients showed hypersensitivity. No previous study has determined the rate of prevalence of salicylate food allergy by application of the oral challenge test in nasal polyposis patients. Some studies have mentioned a significant role of food allergy, not specifically salicylate, in pathogenesis of nasal polyposis. Yet, most surveys used skin tests to evaluate the IgE mediated food allergy in spite of the fact that the gold standard is OFC (25,26). Thus, this study can be applied as a guide further research assessing the role of allergy to salicylate containing food in nasal polyposis. This has also been compared between cases of recurrent and non-recurrent NP. However, no significant difference was determined. This should also be considered in any future research.

Sommer *et al.* detected that a diet low salicylate containing food can improve nasal symptoms and endoscopic findings of patients with AERD (27). This research has provided indication to see if salicylate food allergy was significantly different between patients with nasal polyposis with AERD and cases of non-AERD. Results showed that salicylate food allergy was significantly higher in NP cases with AERD than aspirin tolerant patients ( $p$ -value  $0.019 < 0.05$ ). However, comparing allergic reactions for each individual food did not show any significant difference between the two groups. Nevertheless, further study is needed that applies a higher number of cases in order to properly assess this relationship.

One limitation of this study was missing data due a lack of direct access to patients, especially for performing the oral food challenge test. In spite of this limitation, we could perform a multi-center survey on a higher number of nasal polyposis cases in comparison with previous studies. We introduced a new hypothesis on difference in allergy occurrence between recurrent and non-recurrent nasal polyposis that was clinically assessed for the first time. However, further clinical study is needed to confirm the hypothesis.

Results of this study suggested that atopy and NSAID exacerbated respiratory disease as two possible predictors of NP recurrence. Salicylate food intolerance was also shown to have an associated with AERD in NP.

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