

# The prevalence of aspirin hypersensitivity in patients with nasal polyposis and contributing factors

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## ABSTRACT

**Background:** Aspirin (acetylsalicylic acid [ASA]) hypersensitivity is frequent in patients with nasal polyps (NPs) and is called aspirin exacerbated respiratory disease, previously known as Samter's syndrome. However, studies evaluating the prevalence of ASA hypersensitivity in patients with NPs using the oral aspirin provocation test (APT) are quite limited. This study was designed to determine the prevalence of ASA hypersensitivity and factors associated with ASA hypersensitivity in patients with NPs.

**Methods:** Sixty-eight patients with NPs with or without asthma were recruited. Extension of NPs was evaluated by endoscopic examination/paranasal CT. A 2-day, single-blind placebo-controlled APT was used to detect ASA hypersensitivity.

**Results:** APT was performed in 53 (21 women/ 32 men) patients (mean age,  $39.34 \pm 1.76$  years). APT resulted positive in 12 patients (22.6%) of whom 3 (25%) had no history of ASA hypersensitivity. Of the positive APTs, three were isolated rhinitis and nine had classic responses. APT was negative in 41 patients (77.4%) although three (7.3%) had a history of ASA hypersensitivity. History of ASA hypersensitivity and prolonged duration of NPs were associated with positive APT ( $p < 0.05$ ). Advanced NP with multiple operations was also correlated with APT positivity but was not statistically significant. Presence of asthma was associated with age, female gender, NP duration, and ASA hypersensitivity history ( $p < 0.05$ ), but not with smoking, atopy, NP extension, and positive APT.

**Conclusion:** ASA hypersensitivity is quite common in patients with NP. Patients with extensive and long-term NP with multiple polyp operations require evaluation for the presence of ASA hypersensitivity in terms of chronic management and future risks of the disease.

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Aspirin (acetylsalicylic acid [ASA]) and other nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most widely used drugs because of their analgesic and anti-inflammatory properties. However, a variety of adverse reactions related to ASA/NSAIDs consumption have frequently been reported.<sup>1</sup> Some of these reactions are called ASA hypersensitivity. The clinical presentations of ASA hypersensitivity vary from nasal reaction to severe systemic reaction. The prevalence of ASA hypersensitivity varies according to the study group and method used for the diagnosis of ASA sensitivity.<sup>2,3</sup>

Nasal polyposis is a chronic inflammatory disease of the nose and sinus mucosa that affects up to 4% of the population even though its prevalence has been found to be as high as 40% in cadaveric studies.<sup>4</sup> Nasal polyps (NPs) are often associated with asthma and other diseases, such as cystic fibrosis and ASA hypersensitivity. The association of NPs with ASA hypersensitivity has been a well-recognized clinical entity for a long time and is a challenging disease for both the ear-nose-throat (ENT) specialist and the allergist. NP with ASA hypersensitivity is associated with more severe disease, thus causing a significant impairment in the patients' quality of life. Clinical management of ASA-sensitive NPs is complicated by refractoriness to medical and surgical treatment. The presence of ASA hypersensitivity in these patients has been associated with an increased risk for post-operative complications and a high recurrence rate of polyps.<sup>4–6</sup> There is increasing evidence that ASA desensitization should be considered as an add-on treatment in these patients because this treatment may reduce nasal symptoms and patients' requirements for polypectomy

and/or sinus operations.<sup>1,2,7</sup> Additionally, ASA hypersensitivity may be a risk factor for developing asthma in this group of patients.<sup>7,8</sup> Therefore, an accurate diagnosis of ASA hypersensitivity through appropriate methods in patients with NPs would clearly be welcome. Currently, the only way to accurately diagnose ASA hypersensitivity seems to be through provocative challenge tests with ASA<sup>9,10</sup> because no *in vitro* method has been proven sufficiently sensitive and specific for use as a provocative challenge test.<sup>11–13</sup>

Considering these facts collectively, an acceptable diagnosis of ASA hypersensitivity in patients with NPs seems to be important in terms of chronic management and future risks of the disease. There are many studies regarding the prevalence of NPs in patients with ASA hypersensitivity; however, only a limited number of studies are available evaluating the prevalence of ASA hypersensitivity in patients with NPs, particularly those using an oral aspirin provocation test (APT).<sup>14,15</sup> Additionally, to the best of our knowledge, there is no study in medical literature in English that has systematically evaluated the risk factors associated with ASA hypersensitivity in patients with NPs. Therefore, in this prospective study, we aimed to (1) evaluate the prevalence of ASA hypersensitivity in patients with NPs using oral APT and (2) determine the factors associated with positive oral APT in these patients.

## MATERIALS AND METHODS

### Patient Selection

All adult patients with a suggestive history of NPs with or without asthma were screened and included in this prospective study. Because oral ASA provocations were performed for research purposes for some patients, approval of the local ethical committee was obtained for this group. The rest of the patients were assured of the voluntary nature of the study and all gave written informed consent for oral APT.

### Evaluation of NPs

All patients were examined by an ENT specialist at the ENT Clinic. The duration of NP was based on self-reported data. It was defined as the period between the first diagnoses of NP by an ENT specialist to

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the time that the patient was seen by an ENT specialist participating in this study. The diagnosis of NPs was based on the visualization of bilateral polyps in the nasal cavities by either endoscopic examination or by a CT scan of the paranasal sinuses. The ENT specialists staged each patient by nasal endoscopy based on the De Gaudermar staging system.<sup>16</sup> This system scores stage 0, no polyp; stage 1, polyps are limited at the middle meatus; stage 2, polyps beyond the middle meatus but not completely obstructing the nasal cavity; and stage 3, polyps completely obstructing the nasal cavity.

## Evaluation of Atopy

Atopy was defined as a positive skin-prick test to at least one of the aeroallergens. Glycerinated extracts (Stallergenes, Antony, France) of the following allergenic sources were used in skin-prick tests: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach, grass, tree, weed pollens, cat, dog, and *Alternaria* and *Cladosporium* antigens. Positive (histamine, 10 mg/mL) and negative (saline solution) controls were also included. The puncture method with a 1-mm-tip disposable lancet was used, and a wheal reaction with a mean diameter of 3 mm greater than the negative control was considered a positive response.

## Nonspecific Bronchial Provocation Test

Nonspecific bronchial hyperreactivity (BHR) was evaluated with a methacholine (M) bronchial provocation test, performed according to the method described by Cockcroft *et al.*<sup>17</sup> The result was expressed as PC<sub>20</sub> to M (provocative concentration required to produce a 20% fall in forced expiratory volume in 1 second [FEV<sub>1</sub>]). The M PC<sub>20</sub> was calculated from the log concentration–response curve by linear interpolation of the two last points. A PC<sub>20</sub> to M of  $\leq 8$  mg/mL was accepted as the cutoff point.<sup>18</sup>

## Oral ASA Provocation Test

The oral ASA provocation test was performed according to Nizankowska *et al.*<sup>19</sup> with responses classified as negative, upper airway reaction, classic reaction, and systemic reaction. Upper airway reaction was defined as the presence of rhinorrhea and nasal congestion; classic reaction as more than a 20% decrease in FEV<sub>1</sub> associated with upper airway reaction; and systemic reaction as extra bronchial symptoms such as hoarseness, redness of the face and the upper chest, ocular injection and/or periorbital swelling, nausea, vomiting and stomach cramps, and hypotension with or without cutaneous /bronchial symptoms. A starting dose of 10 mg was followed by 17, 44, 117, and 312 mg of ASA every 1.5–2 hours until a cumulative dose of 500 mg was reached. The provocation test was considered positive if the FEV<sub>1</sub> value decreased by at least 20% from a postsaline baseline value and/or if strong extra bronchial symptoms occurred. The provocative dose of ASA, causing a 20% fall in FEV<sub>1</sub> (PD<sub>20</sub>), was calculated as the PD<sub>20</sub> ASA oral.<sup>19</sup>

## Statistical Analysis

Numeric values were expressed as mean  $\pm$  SEM and categorical/ordinal values were expressed as *n* (%). Further statistical evaluation was performed for comparison of patients with NPs and ASA hypersensitivity and patients with NP and without ASA hypersensitivity. Two group comparisons were performed by independent samples *t*-test, chi-square test, Wilcoxon signed-rank test, and Mann-Whitney *U* test. A value of *p* < 0.05 was accepted as statistically significant for all tests. The Statistical Package for Social Sciences (SPSS) for Windows Version 11.0 (SPSS, Inc., Chicago, IL) was used to analyze the data.

## RESULTS

A total of 68 subjects with NPs were enrolled into the study, but 15 patients were excluded due to withholding their consent for oral APT

**Table 1 Demographic characteristics of the patients who performed oral aspirin provocation test (APT) (*n* = 53)**

|                                               |                           |
|-----------------------------------------------|---------------------------|
| Gender (F/M)                                  | 21/32                     |
| Age, mean $\pm$ SEM (range), yr               | 39, 34 $\pm$ 1.76 (15–70) |
| Atopy, <i>n</i> (%)                           | 19 (35.8%)                |
| Duration of NPs, yr (range)                   | 4.09 $\pm$ 0.82 (0–27)    |
| Newly diagnosed NP/recurrent NP ( <i>n</i> )  | 19/34                     |
| Extension of NP, <i>n</i> (%)                 |                           |
| Stage I                                       | 11 (20.8%)                |
| Stage II                                      | 22 (41.5%)                |
| Stage III                                     | 20 (37.7%)                |
| No. of polypectomies, <i>n</i> (%; range)     | 0–6                       |
| None                                          | 30 (56.7%)                |
| 1                                             | 15 (28.3%)                |
| >2                                            | 8 (15.1%)                 |
| PC <sub>20</sub> to M < 8 mg/mL, <i>n</i> (%) | 24 (45.3%)                |
| Asthma, <i>n</i> (%)                          | 19 (35.8%)                |
| Positive oral APT, <i>n</i> (%)               | 12 (22.6%)                |

NP = nasal polyp; M = methacholine.

or because of their current medical status. The remaining 53 patients (mean age, 39.34  $\pm$  1.76 years) constituted the study population. Demographic data and clinical presentations of the study group are given in Table 1. Male gender was prominent in the study group and 35.8% of the patients with NPs had accompanying asthma. Atopy ratio was 34.8% in the study group and this ratio was not statistically different from that of the general adult population in Turkey (35.8% versus 25%; *p* > 0.05).<sup>20</sup> As far as the NP severity was concerned, 11, 22, and 20 patients were classified as stage I, stage II, and stage III disease, respectively. Only atopic status was found to be related with extension of NPs because 52.9% of nonatopic patients had stage 3 NPs, whereas 57.9% of atopic patients had stage 2 NPs (*p* = 0.009). The presence of BHR to M and a history of ASA hypersensitivity were not associated with the extension of NPs. Thirty patients had never experienced polypectomy, but eight patients had been operated on more than twice. The maximum number of operations for NPs was six times in a 62-year-old woman with a classic ASA triad including NPs, asthma, and ASA hypersensitivity; 45.5% of the patients with NPs resulted in positive bronchial provocation tests to M, with a PC<sub>20</sub> to M  $\leq 8$  mg/mL. The mean age of patients (43.29  $\pm$  2.89 versus 36.06  $\pm$  2.00; *p* = 0.04) was significantly higher, duration of NP (6.08  $\pm$  1.54 versus 2.44  $\pm$  0.67; *p* = 0.03) was significantly longer, and female gender was more common (71.4% versus 28.1%; *p* = 0.002) in patients with BHR to M when compared with those without BHR to M. Atopic status, extension of NPs, number of sinus operations, and history of ASA hypersensitivity were not associated with BHR.

There were 12 patients with a history of ASA/NSAIDs hypersensitivity, but 9 of them resulted in positive oral APT. In contrast, there were 42 patients without a history of ASA hypersensitivity and 3 of them resulted in positive oral APT. As a result, ASA hypersensitivity was confirmed in 12 (22.6%) patients of whom 3 (25%) had no history of ASA hypersensitivity. The details of the patients diagnosed as having ASA hypersensitivity *via* oral APT are shown in Table 2. Of the patients with positive oral APTs, three reacted with isolated rhinitis and nine had a classic response, including both asthma and rhinitis, with a PD<sub>20</sub> ASA ranging from 27 to 500 mg. Although three of the patients had been recently diagnosed as having NPs, the duration of NP ranged from 1 to 20 years in the remainder of the patients. The majority (8/12) were suffering from extensive NPs.

Patients were divided into two groups according to their response to oral APT, *i.e.*, APT<sup>–</sup> and APT<sup>+</sup>, to evaluate the factors associated with ASA hypersensitivity in NPs (Table 3). There were no differences between the two groups in terms of gender, age, and atopy ratio (*p* > 0.05), but history of ASA hypersensitivity and duration of NPs

Table 2 Details of patients with positive oral aspirin provocation test

| n, Age (yr)/Sex | Duration of NP (yr) | Extension of NP (stage) | Polypectomy (no.) | PC <sub>20</sub> to M <8 mg/mL | Asthma Diagnosis | History of ASA Hypersensitivity | PD <sub>20</sub> ASA (mg) |
|-----------------|---------------------|-------------------------|-------------------|--------------------------------|------------------|---------------------------------|---------------------------|
| 1. 29/M         | ND                  | B, 2                    | 0                 | —                              | —                | NSAID                           | NR                        |
| 2. 42/M         | 20                  | B, 3                    | 5                 | +                              | +                | NSAID                           | 140                       |
| 3. 58/M         | ND                  | B, 3                    | 0                 | —                              | —                | —                               | NR                        |
| 4. 62/F         | 20                  | B, 3                    | 6                 | +                              | +                | ASA, NSAID, M                   | 27                        |
| 5. 56/M         | 12                  | B, 2                    | 3                 | —                              | —                | ASA                             | 500                       |
| 6. 33/F         | 13                  | B, 3                    | 2                 | +                              | +                | ASA, NSAID, M                   | 500                       |
| 7. 43/F         | 2                   | B, 3                    | 0                 | +                              | +                | NSAID, P                        | 43                        |
| 8. 33/M         | 8                   | B, 2                    | 1                 | —                              | —                | —                               | 185                       |
| 9. 16/M         | ND                  | B, 2                    | 0                 | —                              | —                | —                               | NR                        |
| 10. 45/F        | 7                   | B, 3                    | 1                 | +                              | +                | ASA, NSAID,                     | 180                       |
| 11. 30/M        | 1                   | B, 3                    | 1                 | —                              | —                | ASA                             | 44                        |
| 12. 30/F        | 1                   | B, 3                    | 1                 | +                              | +                | NSAID                           | 98                        |

APT = aspirin provocation test; NP = nasal polyp; ND = newly diagnosed; B = bilateral; ASA = acetylsalicylic acid; NSAIDs = nonsteroidal anti-inflammatory drugs; M = metamizol; PD<sub>20</sub> ASA = the provocative dose of ASA, causing a 20% fall in FEV<sub>1</sub> (PD<sub>20</sub>); NR = nasal response, FEV<sub>1</sub> = forced expiratory volume in 1 s.

Table 3 Comparison of patients according to oral aspirin provocation test (APT) results

| Characteristics                         | APT <sup>-</sup> n = 41 | APT <sup>+</sup> n = 12        | p Value |
|-----------------------------------------|-------------------------|--------------------------------|---------|
| Gender (F/M)                            | 16/25                   | 5/7                            | 1       |
| Age, mean ± SEM, yr (range)             | 19.34 ± 1.96 (17–70)    | 39.08 ± 4.14 (15–62)           | 0.89    |
| Atopy, n (%)                            | 16 (39%)                | 3 (25%)                        | 0.5     |
| Newly diagnosed NP/recurrent NP         | 16/25                   | 3/9                            | 0.37    |
| Duration of NP, mean ± SEM, yrs (range) | 3.24 ± 0.82 (0–27)      | 9.33 ± 2.49 Classical response | 0.009   |
| Extension of NP, n (%)                  |                         |                                |         |
| Stage I                                 | 11 (26.8%)              |                                |         |
| Stage II                                | 18 (43.9%)              | 4 (33.3%)                      | *       |
| Stage III                               | 12 (29.3%)              | 8 (66.7%)                      |         |
| No. of operation, n (%; range)          | 0–3                     | 0–6                            |         |
| None                                    | 26 (63.4%)              | 4 (33.3%)                      |         |
| 1                                       | 11 (26.8%)              | 4 (33.3%)                      | *       |
| >2                                      | 4 (9.8%)                | 4 (33.3%)                      |         |
| PC <sub>20</sub> to M < 8 mg/mL, n (%)  | 18 (43.9%)              | 6 (50%)                        | 0.7     |
| Asthma, n (%)                           | 13 (31.7%)              | 6 (50%)                        | 0.24    |
| History of ASA hypersensitivity         | 3 (7.3%)                | 9 (75%)                        | 0.000   |

\*Data were not sufficient for chi-square analysis.

ASA = acetylsalicylic acid; FEV<sub>1</sub> = forced expiratory volume in 1 s; NP = nasal polyp; M = methacholine; PC<sub>20</sub> = provocation concentration required to produce a 20% fall in FEV<sub>1</sub>.

were found to be associated with a positive response to oral APT ( $p < 0.05$ ). History of multiple polypectomies and an extension of NPs were also correlated with oral APT, but these results did not attain statistical significance. Although there were a number of patients with all stages of NPs in the APT<sup>-</sup> group, patients with positive APT had only stages 2–3 of NPs. A total of 19 patients with NPs were diagnosed as having asthma associated with age ( $p = 0.02$ ), female gender ( $p = 0.009$ ), duration of NPs ( $p = 0.029$ ), and a history of ASA hypersensitivity ( $p < 0.011$ ).

## DISCUSSION

Reaction to ASA is quite rare in the healthy population (0.3–0.9%); however, the prevalence of ASA hypersensitivity changes in a group of clinical conditions including NPs, asthma, and chronic urticaria. ASA hypersensitivity has been reported in 8–26% of patients with NPs, 10–20% of adult patients with asthma, and 23–28% of patients with chronic urticaria.<sup>21–24</sup> Accordingly, the prevalence of ASA hypersensitivity was found to be 22.6% by applying APT in our patients with NPs.

ASA hypersensitivity is an over- or underdiagnosed phenomena. This was also the case in the current study because 25% of the patients with a history of ASA hypersensitivity resulted in negative APT. In contrast, 7% of patients without a history of ASA hypersensitivity resulted in positive APT. In a study with 50 aspirin exacerbated respiratory disease (AERD) who gave a prior history of aspirin- or NSAID-associated respiratory reactions, 16% did not react to aspirin during oral APT.<sup>25</sup> Once developed, ASA hypersensitivity remains throughout life although a sporadic disappearance of hypersensitivity has been reported.<sup>26</sup> Both overdiagnosis and underdiagnosis of AERD are problems. This issue has been further supported by a recent review in which the prevalence of ASA-sensitive asthma was reported to be 21% in adults when determined by APT; this was contrary to the prevalence of 3–5% reported by verbal history.<sup>27</sup> The reasons for underreporting ASA hypersensitivity may include the deliberate evasion of ASA reporting by patients aware of the risk of adverse reactions or lack of recognition by patients with mild ASA-induced reactions because of their delayed onset of reaction. A multicenter study showed that 15% of asthmatic patients were unaware of

ASA hypersensitivity before challenging with ASA.<sup>28</sup> All these data clearly indicate that ASA hypersensitivity needs to be confirmed by provocation testing. We could not find a study particularly designed to determine ASA hypersensitivity by oral APT in patients with NPs in the English literature. Only one study evaluated the prevalence of subclinical ASA hypersensitivity by inhaled lysine ASA in subjects with NPs and found that in the absence of clinical history, only a small proportion of patients (9.3%) are likely to be sensitive to ASA.<sup>15</sup> In our trial, 3 (25%) of 12 patients who reacted to APT had no history of ASA hypersensitivity, and 2 patients with a history of ASA hypersensitivity did not respond to oral APT.

Data concerning the reaction pattern to oral APT of patients with NPs is very limited. Eichel *et al.* showed that 15% of patients with NPs have a bronchospastic type of ASA hypersensitivity and this prevalence increases to 60% of patients with a frequent recurrence of NPs after surgery.<sup>14</sup> In our 12 ASA hypersensitive patients, 3 with NPs, without asthma (25%), reacted with isolated rhinitis and another 3 patients with NPs, without asthma (25%), showed a classic response, including both asthma and rhinitis to oral APT. Although the number of patients is a little too limited to make a strong comment on that issue, patients with NPs, in the absence of AERD, can also show bronchial response to oral APT as well as isolated rhinitis.

It has repeatedly been reported that patients with NPs and ASA hypersensitivity have more severe sinonasal disease and a significantly higher need for revision surgery than ASA-tolerant patients.<sup>6,29,30</sup> In keeping with this finding, our patients with ASA hypersensitivity were also more severe in terms of extension of NPs and had undergone a higher number of sinus surgeries. ASA desensitization is an option for these patients. Long-term studies have shown the efficacy of ASA desensitization in reducing nasal symptoms, the recurrence of sinusitis, and NP formation.<sup>7,24,26</sup>

To the best of our knowledge, the factors associated with ASA hypersensitivity in patients with NPs have not been systematically evaluated to date. Although the numbers of patients with ASA hypersensitivity is limited in our trial, a history of ASA hypersensitivity and prolonged durations of NPs appeared to be risk factors associated with ASA hypersensitivity. Although they did not attain the level of statistical significance, an advanced stage of NPs and a history of multiple operations were also correlated with a positive APT response, supporting the findings of Eichel *et al.*<sup>14</sup> On the other hand, there was no difference in the age, gender, asthma prevalence, and atopy ratio of our NP patients with or without ASA hypersensitivity, a finding that concurs with previous reports.<sup>31,32</sup> Although a number of clinical studies have challenged the role of allergy as a causative factor in NPs, positive skin-prick test results were no more common in patients with NPs than they were in the general adult population in Turkey. This indicates that the presence of atopy is coincidental rather than causative, a finding that also supports our data.<sup>21,33,34</sup>

The association between NPs and lower airway disease, such as asthma and asymptomatic nonspecific BHR, has been the subject of several studies. The frequency of asthma in patients with NPs ranges from 7 to 70%.<sup>32,35</sup> A complete clinical picture of the ASA triad, including ASA hypersensitivity and asthma, was found in as many as 20% of cases with NPs.<sup>24,31</sup> One-half of the patients with NPs in our trial had a complete ASA triad. Nonspecific BHR and changes of pulmonary function parameters have been documented in patients with NPs.<sup>36</sup>

A very recent study reported that the presence of NPs in patients with allergic rhinitis appeared as an independent risk factor for BHR.<sup>37</sup> The significance of asymptomatic BHR associated with NPs is unknown but it may represent an indication of potential asthma. Patients with NPs were followed over a 4-year period to evaluate the long-term evolution of nonspecific BHR/pulmonary function, and the study indicated that steroid-nonresponsive NPs treated by nasal surgery are associated with progressive FEV<sub>1</sub> decline and the appearance of airflow obstruction even though BHR did not significantly change over this period.<sup>38</sup> In our study, there were 24 patients (45.3%)

with a PC<sub>20</sub> to M < 8 mg/mL. Among them, six patients had ASA hypersensitivity and a clinical diagnosis of asthma. Thirteen of the remaining 18 patients had asthma without ASA hypersensitivity, and 5 patients had asymptomatic BHR. In our trial, ASA hypersensitivity did not appear as a risk factor for the development of asthma in patients with NPs. However, considering the nonresponsive nature to steroids and frequent surgical requirement of ASA-sensitive NPs, further long-term follow-up studies with a higher numbers of patients with ASA hypersensitivity are clearly needed. In conclusion, taking into account the less favorable long-term outcomes of NPs with ASA hypersensitivity and the potential role of ASA desensitization as an alternative treatment in preventing the recurrence of NPs, the presence of ASA hypersensitivity should be considered to improve chronic management and raise awareness of future risks.

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