Clinical Features and Patient-Reported Control of Respiratory Tract and Ear Symptoms in NSAID-Exacerbated Respiratory Disease (N-ERD) - A Retrospective Cross-Sectional Questionnaire Study

Anna Suikkila[1], Lena Hafrén[1], Annina Lyly[1], tuomas klockars[1], and Riitta Saarinen[1]

[1]Helsinki University Central Hospital Head and Neck Center

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Abstract

ABSTRACT Objective We assessed the prevalence, clinical characteristics, and severity of respiratory tract and ear symptoms among Finnish Non-steroidal anti-inflammatory drug (NSAID) exacerbated respirato-ry disease (N-ERD) patients. Design A retrospective cross-sectional questionnaire study. Setting A university tertiary care center. Participants A total of 232 patients with both asthmatic and polypoid ICD-10 diagnoses treated at our universi-ty tertiary care center between January 2016 and May 2017 were identified by an electronic patient record search. The patient charts were manually reviewed and 102 patients with speci-fied symptoms on NSAID exposure, in addition to asthma and nasal polyposis diagnosis, were considered potential N-ERD patients. The patients received a questionnaire with an informed consent form, and the 66 patients who responded and confirmed diagnoses of asthma, nasal polyposis, and acetylsalicylic acid (ASA) or NSAID intolerance were included. Results The first diagnosis received was asthma, followed by NSAID intolerance and nasal polyposis, when evaluated by mean age of contracting the condition. When evaluating individual patients, there was considerable variation in the order and timing of the separate conditions. The majority of the patients received all three diagnoses within a few years' time. The diagnostics and treat-ment of N-ERD patients seemed to only partially follow the international guidelines. The propor-tion of N-ERD patients with recurrent or chronic middle ear infection was 18%. Patient-reported disease control was good in asthma, but only mediocre in nasal polyposis and ear symptoms. As many as 14% reported a positive family history of N-ERD. Conclusions Structured cross-department diagnostics and care could benefit N-ERD patients in Finland. Rhi-nological and aural symptoms seem to affect a patient's quality of life more than asthma. The high proportion of familial cases warrants further studies. Keywords: Asthma, Aspirin-Induced, Nasal Polyps, Aspirin, NSAIDs, Heredity, Ear, Middle, Fin-land

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Design

A retrospective cross-sectional questionnaire study.

Setting

A university tertiary care center.

Participants

A total of 232 patients with both asthmatic and polypoid ICD-10 diagnoses treated at our university tertiary care center between January 2016 and May 2017 were identified by an electronic patient record search. The patient charts were manually reviewed and 102 patients with specified symptoms on NSAID exposure, in addition to asthma and nasal polyposis diagnosis, were considered potential N-ERD patients. The patients received a questionnaire with an informed consent form, and the 66 patients who responded and confirmed diagnoses of asthma, nasal polyposis, and acetylsalicylic acid (ASA) or NSAID intolerance were included.

Results

The first diagnosis received was asthma, followed by NSAID intolerance and nasal polyposis, when evaluated by mean age of contracting the condition. When evaluating individual patients, there was considerable variation in the order and timing of the separate conditions. The majority of the patients received all three diagnoses within a few years' time. The diagnostics and treatment of N-ERD patients seemed to only partially follow the international guidelines. The proportion of N-ERD patients with recurrent or chronic middle ear infection was 18%. Patient-reported disease control was good in asthma, but only mediocre in nasal polyposis and ear symptoms. As many as 14% reported a positive family history of N-ERD.

Conclusions

Structured cross-department diagnostics and care could benefit N-ERD patients in Finland. Rhinological and aural symptoms seem to affect a patient's quality of life more than asthma. The high proportion of familial cases warrants further studies.

Keywords: Asthma, Aspirin-Induced, Nasal Polyps, Aspirin, NSAIDs, Heredity, Ear, Middle, Finland

KEY POINTS

- N-ERD is an eosinophilic inflammatory disease of the upper and lower airway mucous membranes characterized by the co-existence of asthma, nasal polyposis and hypersensitivity to NSAIDs.
- We present the clinical characteristics and patient-assessed disease control of N-ERD in our university tertiary care center in Finland with special emphasis on ear symptoms.
- The diagnostics and treatment of N-ERD patients in our study group seemed to only partially follow the international guidelines.
- Ear symptoms were common and the majority of the ear-symptomatic patients had needed an intervention to control their symptoms.
- The patient-assessed control of nasal polyposis and ear symptoms was poorer than the control of asthma symptoms.

1. INTRODUCTION

Non-steroidal anti-inflammatory drug (NSAID) -exacerbated respiratory disease (N-ERD) is an adult-onset inflammatory disease of the upper and lower respiratory mucous membranes characterized by the co-existence of asthma, nasal polyposis, and sensitivity to NSAIDs. The spectrum was originally described by Samter and Beers in 1968.[1,2]It was formerly referred to as aspirin-exacerbated respiratory disease (AERD) or Samter's Triad. Since hypersensitivity comprises not only aspirin but also other cyclo-oxygenase-1 (COX-1) inhibitors, the term N-ERD is more accurate for describing the disorder [3].

The prevalence of N-ERD is suggested to be 0.3-0.9% in the general population. The prevalence is higher among patients with asthma (7%), chronic rhinosinusitis with nasal polyps (10%), or severe asthma (15%)[4-6], and is up to 30% in asthmatics with nasal polyposis [7]. In most studies, rhinitis symptoms are the presenting feature. Generally, in about five years' time the diagnosis of asthma is set, with symptoms of NSAID intolerance subsequently leading to a diagnosis of nasal polyposis.[8] The clinical course of asthma and nasal polyposis is often severe [3,4,9-11]. However, patients' subjective experience of disease control and quality of life is better than expected [12,13].

N-ERD has been proposed to be acquired with unknown epigenetic triggers combined with underlying genetic predisposition. The clinical presentation in adulthood and lack of replication in genetic studies together with the continuing upper and lower respiratory mucosal inflammation independent of aspirin exposure indicate that epigenetic mechanisms may contribute more to the pathogenesis than genetic variations [14]. The chronic eosinophilic inflammation of the upper and lower airway mucous membranes is known to be related to disturbances in arachidonic acid metabolism. Arachidonic acid is the precursor of the inflammation mediators leukotrienes and prostaglandins[3,15,16].

International recommendations for diagnostics and treatment options for N-ERD include multimodal disease-specific treatment[3,17]. Inhaled corticosteroids with long-acting beta-2 agonists and leukotriene-modifying drugs (LTMD) are the treatment of preference for N-ERD-related asthma. Biologic anti-IgE therapy with omalizumab and regular peroral corticosteroids are reserved for severe cases. Daily saline irrigation and topical corticosteroid drops are basic treatments for nasal polyposis accompanied by short courses of peroral corticosteroids. Sinonasal polypectomy and functional endoscopic sinus surgery are warranted in cases with uncontrolled symptoms despite adequate medication [17]. LTMD also relieves nasal symptoms. Omalizumab and the biologics targeting eosinophilic inflammation (mepolizumab, reslizumab, dupilumab) are effective options for recurrent operations and corticosteroid courses. Aspirin desensitization is an effective option for both nasal polyposis and asthma. The disease control is often challenging, and multimodal treatment with recurrent surgical procedures is frequently needed[4,18,19].

One-quarter (26%) of N-ERD patients exhibit ear symptoms such as aural fullness, otorrhea, and conductive hearing loss [20]. There are a few case reports of binaural middle ear polyposis among female N-ERD patients [21]. Interestingly, the histology of middle ear polypoid mass biopsies is similar to the nasal polyps seen in N-ERD [22]. If present, symptoms of otitis media with effusion usually develop subsequent to other manifestations of N-ERD[23].

The aim of this study was to assess the clinical characteristics and patient-reported severity of symptoms of N-ERD in the Finnish population. In addition, we wanted to evaluate the presence and severity of coexisting chronic or recurrent middle ear infections.

1.1 ETHICAL CONSIDERATIONS

The study protocol was approved by the [removed for blind peer review][1] Ethics Committee ([removed for blind peer review][2]/3078/2017). The authors of this article declare no conflict of interest.

2. MATERIALS AND METHODS

[removed for blind peer review][3] is a tertiary referral center providing healthcare services for [removed for blind peer review][4] inhabitants. The [removed for blind peer review][5] electronic patient records cover all medical specialties, excluding primary healthcare.

We conducted a retrospective database search for patients with ICD-10 diagnoses of asthma (J45.0, J45.1, J45.8, J45.9) and nasal polyposis (J33.0, J33.1, J33.8, J33.9) between January 2016 and May 2017. Patient charts were manually reviewed to identify patients with clinical history and symptoms of NSAID intolerance. Aspirin challenge was not required. A questionnaire with informed consent was sent to patients with suspected N-ERD. The non-respondents were sent a new questionnaire and informed consent once. Patients returning the questionnaires between April 2018 and May 2019 and all returned questionnaires were analyzed.

In the questionnaire, patients were first asked to confirm having diagnoses of asthma, nasal polyposis, and NSAID intolerance. Only patients confirming these conditions were included. In addition, we asked about current medication for asthma and nasal polyposis, number of recent oral corticosteroid courses, surgical history for nasal polyposis, and family history of asthma, nasal polyposis, NSAID intolerance, or N-ERD. We also asked patients to assess the current control of their symptoms, their NSAID exposure-related symptoms, and the presence and control of ear symptoms. We focused on a subgroup of patients confirming adult-onset recurrent or chronic middle ear infection and analyzed them separately.

Associations between patient characteristics and clinical variables were calculated using Fisher exact tests. A

P-value < 0.05 was considered statistically significant. Descriptive statistics were used for means, medians, and ranges. In this study we followed the STROBE reporting guideline for observational studies.

3. RESULTS

The patient retrieval process is summarized in Figure 1. A total of 232 patients had ICD-10 diagnoses for both asthma and nasal polyposis. After manual review of patient charts, we identified 102 patients (102/232, 44%) with a clinical history of NSAID intolerance. These patients were considered possible N-ERD patients, and they received the questionnaire and informed consent form. Seventy patients (70/102, 69%) responded and the inclusion criteria (confirmed asthma, nasal polyposis, and NSAID intolerance) were met by 66 respondents (66/70, 94%). Their demographic characteristics are shown in detail in Table 1. Of the 66 patients, 12 (18%) reported recurrent or chronic middle ear infection.

Based on the inquiry, the diagnoses of asthma, NSAID intolerance, and nasal polyposis were set in a close time frame. The median time span was four years and the average six years. When taking into account only the mean contraction ages, the first diagnosed condition was asthma, followed by NSAID intolerance and nasal polyposis. However, considerable variation existed in the order and timing of the separate conditions for individual patients. Six patients (9%) received all three diagnoses in the same year. The disease-specific contraction time of individual patients is shown in Figure 2.

3.1 ASTHMA

The median age of onset for asthma was 33 years. The majority (94%) of the patients used inhaled corticosteroids. Less than half (38%) took leukotriene modifiers regularly, and only two (3%) had biological medical therapy. Two-thirds (64%) had needed peroral corticosteroid treatment either continuously or as a course in the past five years. The number of corticosteroid courses required varied from 1 to 20. The majority (83%) reported the experienced disease control of asthma to be good or very good. Only 12% reported poor or very poor asthma control. Twelve patients (18%) had had asthma for over 30 years, and four of these (33%) reported poor disease control. Detailed asthma characteristics are presented in Table 1.

3.2 NASAL POLYPOSIS

The median age of onset of nasal polyposis was 34 years. The majority (88%) used topical nasal steroids regularly. Of these, 23 (35%) used corticosteroid drops and the remainder nasal sprays. Nearly all (95%) had undergone surgical removal of nasal polyps, and the number of reported operations varied from 1 to 70. More than half (59%) had needed a course of oral corticosteroids in the past five years. The number of courses varied from 1 to 30. The proportion of patients regarding polyp control to be good or very good was 58%; the corresponding figure for poor or very poor polyp control was 38%. The condition diagnosed first did not affect the reported severity of nasal symptoms. Detailed nasal polyposis characteristics are presented in Table 1.

3.3 ASPIRIN OR NSAID INTOLERANCE

The median age of onset of NSAID intolerance was 35 years. Reported aspirin or NSAID-related symptoms included worsening of asthma (38%), breathing difficulties (86%), swelling, itching, or irritation of oral or pharyngeal mucous membranes (42%), skin symptoms (21%), and other symptoms (32%), including nasal congestion and discharge, sneezing, worsening of polyps, eye irritation, nausea, abdominal pain, and swelling of the face. Anaphylaxis was reported by three patients (5%). None reported exclusively skin symptoms caused by NSAID, which makes NSAID-related urticaria unlikely. Thirty patients (45%) had undergone an aspirin challenge. Twenty-three patients (35%) were further treated with aspirin desensitization between the years 1999 and 2018. Twelve of the desensitized patients (52%) reported relief of symptoms, including decreased growth of nasal polyps, less nasal congestion and discharge, and less shortness of breath and asthma-related symptoms. Two of the challenged but not desensitized patients reported anaphylaxis on NSAID exposure. Aspirin treatment (250 mg) was used by five patients (8%) at the time of inquiry, which is less than half of those who had undergone successful desensitization with relief of their symptoms. Detailed NSAID intolerance characteristics are presented in Table 1.

3.4 EAR SYMPTOMS

Recurrent (more than twice a year) or chronic (more than two months) adult-onset middle ear infections were reported by about one-fifth (12/66, 18%) of patients. The median age of onset was 37 years. Eleven (11/12, 92%) of the ear-symptomatic patients were women ($p = 0.0205$). The number of infections varied from two to over ten in the past five years. Adulthood myringotomy was performed for the majority (9/12, 75%) from one to five times. Over half (7/12, 58%) had been placed on tympanostomy tubes from one to eight times in adulthood. Six patients (50%) reported a history of adulthood tympanic membrane perforation and five reported currently having a tympanic membrane perforation. Two had hearing aids, both bilateral.

The subjective clinical control of ear symptoms was regarded as good or very good by 73% and poor or very poor by 15% of the 66 patients. In contrast, in the recurrent or chronic middle ear infection subgroup the majority (7/12, 58%) regarded the control of ear symptoms as poor or very poor and only one-third (4/12, 33%) as good or very good. Detailed ear symptom characteristics are presented in Table 2.

3.5 FAMILY HISTORY

Positive family history was most common in asthma (56%), followed by nasal polyposis (21%) and NSAID intolerance (9%). Notably, 14% reported a positive family history of N-ERD. For details, see Table 1.

4. DISCUSSION

4.1 KEY RESULTS

This study is the first to describe the clinical characteristics and patient-reported disease control of N-ERD in the Finnish population and one of the largest to describe ear symptoms associated with N-ERD.

When mean onset ages were considered, the first reported diagnosis was asthma, followed by NSAID intolerance and nasal polyposis. The time span for setting all three diagnoses was relatively short, the median time span being four years and the average six years. For 13 patients (20%), all diagnoses had been set within two years. However, for individual patients considerable variation existed in the timing and order of separate diagnoses.

The diagnostics and treatment of N-ERD patients in our study group seemed to only partially follow the international guidelines. Less than half were diagnosed with aspirin challenge or treated with aspirin desensitization, and only a few were on aspirin treatment after desensitization. LTMD was reported to be used by less than half of respondents. Only two had biological anti-IgE medical treatment for asthma, and none had any biological treatment for nasal polyposis despite abundant use of corticosteroid courses for both asthma and nasal polyposis and numerous surgical procedures for nasal polyp control. Patient-reported disease control was best in asthma, followed by nasal polyposis and ear symptoms. More efficient follow-up and treatment for nasal polyposis in N-ERD are required.

Ear symptoms were common, with one-fifth (18%) of patients reporting them. The ear-symptomatic patients were mainly women (92%, $p=0.0205$). The majority had needed an intervention of myringotomy or tympanostomy tubes to control their ear symptoms. Almost half had current tympanic membrane perforation, indicating chronic inflammation. Considering the commonness of ear symptoms and needed interventions and the shortages in N-ERD-associated nasal polyposis care, patients would benefit from cross-department diagnostics and care for N-ERD. The patient's perspective of disease control should be taken into account when planning the follow-up and treatment of N-ERD.

Up to 14% of patients reported a positive family history of N-ERD, which warrants further investigations.

4.2. STRENGTHS AND LIMITATIONS OF THE STUDY

Data collection was conducted by a database search for ICD-10 diagnosis codes for asthma and nasal polyposis. Thus, it is possible that some patients not having a registered diagnosis in the database were missed, and the number of patients having both diagnoses might be underestimated in the study. This might have influenced the high proportion (44%) of N-ERD among asthma and nasal polyposis patients. To our knowledge, this is the largest study describing the number and nature of ear symptoms among N-ERD patients.

The study design relies on information collected from patients, thus carrying a risk of reporting bias. Furthermore, we did not require a positive aspirin challenge for the diagnosis of N-ERD. Instead, intolerance was based on registered symptoms by aspirin intake in patient charts and the patient's subjective confirmation of intolerance. However, in previous studies, clinical history of NSAID intolerance appears to be reliable [3,6,24].

Biological monoclonal antibody medication for severe allergic and eosinophilic asthma and nasal polyposis is a relatively recent therapeutic option. Thus, the timing of data collection might have influenced the scarce usage of biological medication in our cohort. Patients' subjective reported disease control could likewise be better with more efficient medication, at least for asthma and nasal polyposis.

4.3 COMPARISON WITH OTHER STUDIES

In this study, the proportion of asthmatic and nasal polyposis patients with NSAID intolerance was relatively high (44%) compared with earlier studies reporting prevalence rates of 30% [7]. Data were collected in a university tertiary care center, excluding primary healthcare, which might have led to a higher prevalence of N-ERD among our asthma and nasal polyposis patients.

In most previous studies, rhinitis symptoms are the presenting feature, with supervening diagnoses of asthma, NSAID intolerance, and nasal polyposis over a time span of about six years.[8] In our study, this was the sequence of the diagnoses when only the mean onset ages were considered. However, when individual patients were viewed separately, remarkable variation existed in the sequence of the separate conditions. The onset age in the fourth decade of life and the female predominance are consistent with data from previous studies[8]. The prevalence of 18% and the female predominance among patients suffering from ear symptoms is similar to the proportion (26%) and sex distribution described earlier [2023]. Ear symptoms might be underrated in the care of N-ERD patients. In our study, multiple interventions were needed for the control of ear symptoms, and ear-symptomatic patients regarded this condition as the worst controlled.

The number of patients reporting a positive family history of N-ERD (14%) was unexpectedly high and warrants further studies. The number of familial cases of N-ERD has previously been markedly lower (1-6%)[8] [9].

4.4 CLINICAL APPLICABILITY OF THE STUDY

N-ERD is a systemic condition and the diagnoses of upper and lower respiratory tract disorders are often set close to each other, albeit usually on separate occasions. Tertiary healthcare may be provided in only the ear, nose, and throat or pulmonary department, delaying the diagnosis of either asthma or nasal polyposis, with the overall picture of the patient's condition being missed. There is a clear demand for structured diagnostics and treatment for this challenging patient group in Finland.

When considering the multimodal diagnostics and therapy recommended for N-ERD, it is crucial to refer all patients to tertiary healthcare for optimal treatment and follow-up, and, even more importantly, the collaboration between different specialties should be enhanced. In our cohort from a university tertiary care center, the N-ERD patients did not appear to have all the diagnostic and therapy options available from which they could derive a benefit. This finding has also recently emerged in a comprehensive register study [25].

The patient-assessed control of nasal polyposis and ear symptoms was poorer than the control of asthma symptoms. Therefore, more emphasis must be placed on controlling these symptoms. According to our findings, nasal symptoms together with chronic ear infection seem to affect the patient's quality of life more than asthma. Whether this is due to inadequate use of medication or more severe disease remains to be evaluated. The ear symptoms, although not an official component of the triad, deserve adequate evaluation and treatment.

4.5 CONCLUSIONS

More accurate N-ERD diagnostics and treatment are needed in Finland. Otological symptoms are common and together with rhinological symptoms are poorer controlled than asthma symptoms. The unexpectedly high number of familial cases warrants further investigations.

5. REFERENCES

5.1 DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

1. Samter M, Beers RF. Concerning the nature of intolerance to aspirin. *J Allergy* . 1967;40(5):281-293.

2. Samter M, Beers RF. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med* . 1968;68(5):975-983.

3. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD)-a EAACI position paper. *Allergy* . 2019;74(1):28-39. doi: 10.1111/all.13599 [doi].

4. Kennedy JL, Stoner AN, Borish L. Aspirin-exacerbated respiratory disease: Prevalence, diagnosis, treatment, and considerations for the future. *Am J Rhinol Allergy* . 2016;30(6):407-413. doi: 10.2500/ajra.2016.30.4370 [doi].

5. Li KL, Lee AY, Abuzeid WM. Aspirin exacerbated respiratory disease: Epidemiology, pathophysiology, and management. *Med Sci (Basel)* . 2019;7(3):10.3390/medsci7030045. doi: E45 [pii].

6. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. *J Allergy Clin Immunol* . 2015;135(3):676-81.e1. doi: 10.1016/j.jaci.2014.08.020 [doi].

7. Steinke JW, Borish L. Factors driving the aspirin exacerbated respiratory disease phenotype. *Am J Rhinol Allergy* . 2015;29(1):35-40. doi: 10.2500/ajra.2015.29.4123 [doi].

8. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE investigators. european network on aspirin-induced asthma. *Eur Respir J* . 2000;16(3):432-436. doi: 10.1034/j.1399-3003.2000.016003432.x [doi].

9. Laidlaw TM. Pathogenesis of NSAID-induced reactions in aspirin-exacerbated respiratory disease. *World J Otorhinolaryngol Head Neck Surg* . 2018;4(3):162-168. doi: 10.1016/j.wjorl.2018.08.001 [doi].

10. Stevens WW, Peters AT, Hirsch AG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* . 2017;5(4):1061-1070.e3. doi: S2213-2198(17)30005-3 [pii].

11. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* . 2002;89(5):474-478. doi: S1081-1206(10)62084-4 [pii].

12. Feldman JM, Zeigler AE, Nelson K, et al. Depression symptoms and quality of life among individuals with aspirin-exacerbated respiratory disease. *J Asthma* . 2019;56(7):731-738. doi: 10.1080/02770903.2018.1490754 [doi].

13. Jang DW, Comer BT, Lachanas VA, Kountakis SE. Aspirin sensitivity does not compromise quality-of-life outcomes in patients with samter's triad. *Laryngoscope* . 2014;124(1):34-37. doi: 10.1002/lary.24220 [doi].

14. Dahlin A, Weiss ST. Genetic and epigenetic components of aspirin-exacerbated respiratory disease. *Immunol Allergy Clin North Am* . 2016;36(4):765-789. doi: S0889-8561(16)30055-8 [pii].

15. Laidlaw TM, Boyce JA. Pathogenesis of aspirin-exacerbated respiratory disease and reactions. *Immunol Allergy Clin North Am* . 2013;33(2):195-210. doi: 10.1016/j.iac.2012.11.006 [doi].

16. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease.*N Engl J Med* . 2018;379(23):2281-2282. doi: 10.1056/NEJMc1813469 [doi].

17. Fokkens WJ, Lund VJ, Hopkins C, et al. Executive summary of EPOS 2020 including integrated care pathways. *Rhinology* . 2020;58(2):82-111. doi: 10.4193/Rhin20.601 [doi].

18. Roland LT, Nagy C, Wang H, et al. Treatment practices for aspirin-exacerbated respiratory disease: Analysis of a national insurance claims database. *Int Forum Allergy Rhinol* . 2019. doi: 10.1002/alr.22471 [doi].

19. Walters KM, Waldram JD, Woessner KM, White AA. Long-term clinical outcomes of aspirin desensitization with continuous daily aspirin therapy in aspirin-exacerbated respiratory disease. *Am J Rhinol Allergy* . 2018;32(4):280-286. doi: 10.1177/1945892418770260 [doi].

20. Caversaccio M, Hausler R, Helbling A. Otologic manifestations in samter's syndrome. *ORL J Otorhinolaryngol Relat Spec* . 2009;71(1):6-10. doi: 10.1159/000163218 [doi].

21. Sethukumar P, Heywood R, Narula A. Samter's triad with aural involvement: A novel approach to management. *J Laryngol Otol* . 2014;128(12):1114-1116. doi: 10.1017/S0022215114002722 [doi].

22. Shen J, Peterson M, Mafee M, Nguyen QT. Aural polyps in samter's triad: Case report and literature review. *Otol Neurotol* . 2012;33(5):774-778. doi: 10.1097/MAO.0b013e318259522f [doi].

23. Hafren L, Pajari M, Vento SI, Saarinen R. Otitis media with effusion in aspirin-exacerbated respiratory disease patients-A series of 22 cases. *Clin Otolaryngol* . 2018;43(5):1387-1391. doi: 10.1111/coa.13150 [doi].

24. Laidlaw TM, Cahill KN. Current knowledge and management of hypersensitivity to aspirin and NSAIDs. *J Allergy Clin Immunol Pract* . 2017;5(3):537-545. doi: S2213-2198(16)30559-1 [pii].

25. Cahill KN, Johns CB, Cui J, et al. Automated identification of an aspirin-exacerbated respiratory disease cohort. *J Allergy Clin Immunol* . 2017;139(3):819-825.e6. doi: S0091-6749(16)30700-X [pii].

6. TABLE AND FIGURE LEGENDS

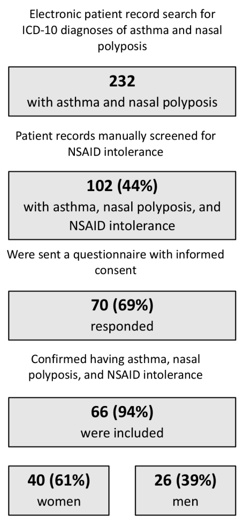
6.1 The Questionnaire

6.2 Figure 1. The Patient retrieving process. NSAID non-steroidal anti-inflammatory drug.

6.3 Table 1. Clinical characteristics of the included 66 patients. + in five past years as a course or regularly. N number of patients. n/a Not answered. ASA acetylsalicylic acid. NSAID non-steroidal anti-inflammatory drug.

6.4 Figure 2. The disease-specific contraction time of the individual patients. Each symbol represents one of the 66 included patients. NSAID non-steroidal anti-inflammatory drug.

6.5 Table 2. Characteristics of the twelve ear-symptomatic patients. N number of patients. n/a Not answered.


Electronic patient record search for ICD-10 diagnoses of asthma and nasal polyposis
232
with asthma and nasal polyposis
Patient records manually screened for NSAID intolerance
102 (44%)
with asthma, nasal polyposis, and NSAID intolerance
Were sent a questionnaire with informed consent
70 (69%)
responded
Confirmed having asthma, nasal polyposis, and NSAID intolerance
66 (94%)
were included
40 (61%)
women
26 (39%)
men

		Mean	Median (Range)	N	%	n/a (%)
Demographic data	**Age (years)**	52	53 (21-73)	66		
	Age, men (years)	51	51 (26-71)	26	39	
	Age, women (years)	52	54 (21-73)	40	61	
Asthma	**Age at onset (years)**	34	33 (3-66)			2 (3)
	Years with phenotype	17	15 (1-48)			
	Set as first diagnosis			38	58	
	Control of disease: good or very good			55	83	3 (5)
	Control of disease: poor or very poor control			8	12	3 (5)
	Positive family history			37	56	8 (12)
	Negative family history			21	32	8 (12)
Nasal polyps	**Age at onset (years)**	36	34 (11-70)			1 (2)
	Years with phenotype	16	12 (1-45)			
	Set as first diagnosis			10	15	
	Surgical removal of nasal polyps			63	95	
	Control of disease: good or very good			38	58	3 (5)
	Control of disease: poor or very poor control			25	38	3 (5)
	Positive family history			14	21	11 (17)
	Negative family history			41	62	11 (17)
NSAID intolerance	**Age at onset (years)**	35	35 (5-65)			6 (9)
	Years with phenotype	16	15 (0-46)			
	Set as first diagnosis			7	11	
	NSAID-related symptoms			64	97	2 (3)
	ASA challenge			30	45	
	ASA desensitization			23	35	
	Successful ASA desensitization			12	18	
	Positive family history			6	9	20 (30)
	Negative family history			40	61	20 (30)
Treatment	**Inhaled corticosteroids**			62	94	
	Leucotriene modifiers			28	42	
	Biologic medical therapy			2	3	
	Topical nasal steroids			59	89	
	Regular peroral ASA 250 mg			5	8	
	Peroral corticosteroids for asthma †			42	64	3 (5)
	No peroral corticosteroids needed for asthma †			21	32	3 (5)
	Peroral corticosteroids for nasal polyps †			39	59	10 (15)
	No peroral corticosteroids needed for nasal			17	26	10 (15)
Ear symptoms	**Control of disease: good or very good**			48	73	8 (12)
	Control of disease: poor or very poor control			10	15	8 (12)
	No hearing aid			57	86	5 (8)
	Bilateral hearing aid			4	6	5 (8)

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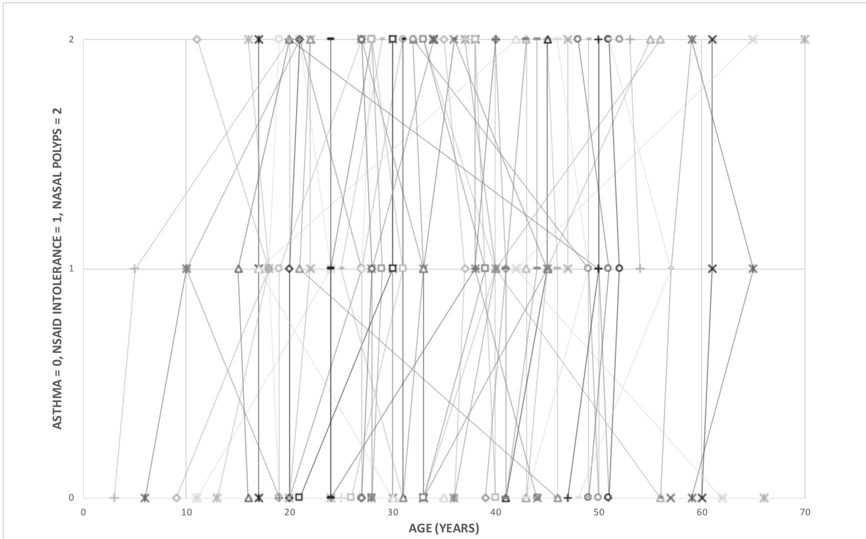
ASTHMA = 0, NSAID INTOLERANCE = 1, NASAL POLYPS = 2
AGE (YEARS)
0
1
2
0
10
20
30
40
50
60
70

	Mean	Median (Range)	N	%	n/a (%)
Age at onset (years)	35	37 (18-51)	12		3 (25)
Adulthood myringotomy			9	75	
Adulthood ventilating tubes			7	58	
Adulthood tympanic membrane			6	50	
Current tympanic membrane perforation			5	42	
Bilateral hearing aid			2	17	
Good or very good clinical control			4	33	1 (8)
Poor or very poor clinical control			7	58	1 (8)

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