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Original Article

Evaluation of Risk Factors Causing Diagnostic Delay in Non-steroidal Anti-inflammatory Drug-exacerbated Respiratory Disease

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Abstract

OBJECTIVE: Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) can be difficult to diagnose due to the heterogeneity of phenotypes and a lack of validated *in vitro* tests. This study aimed to provide a better understanding of the course of N-ERD disease, analyze whether there was a delay in clinical diagnosis, and explore the factors that might cause diagnostic delay.

MATERIAL AND METHODS: This observational, cross-sectional, study included patients aged over 18. The time taken by clinicians to diagnose N-ERD was recorded as the clinician diagnosis time, while the time taken by patients to complete the N-ERD triad was recorded as the actual diagnosis time. A difference of six months or longer between actual diagnosis and clinician diagnosis times was accepted as diagnostic delay. Statistical analyses were performed to ascertain the parameters that could cause this delay.

RESULTS: The study included a total of 107 patients diagnosed with N-ERD. The patients had been diagnosed with chronic rhinosinusitis with nasal polyps, asthma, and NSAID hypersensitivity for an average duration of 14.9±9.6, 14.3±9.9, and 11.7±9.3 years, respectively. Thirty-nine (36.4%) of the patients had a delayed diagnosis. The mean delay in the diagnosis of N-ERD was 7.4±6.6 (2.0-12.0) years. Delayed diagnosis showed a correlation with thyroid dysfunction ($P = 0.021$), while it did not have a significant relationship with the remaining factors.

CONCLUSION: The results of this study have indicated delays in diagnosing N-ERD patients and emphasized the need for adequately recognizing the disease to initiate timely, appropriate treatment.

KEYWORDS: Non-steroidal anti-inflammatory drug-exacerbated respiratory disease, nasal polyp, asthma, aspirin, non-steroidal anti-inflammatory drug hypersensitivity

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INTRODUCTION

Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) is a chronic eosinophilic inflammatory disorder of the respiratory tract that occurs in patients with asthma, chronic rhinosinusitis, and/or nasal polyps (CRSwNP), whose symptoms are exacerbated by NSAIDs.[1] The prevalence of N-ERD increases as the severity of respiratory disease increases, reaching 14.9% in patients with severe asthma and 24% in those admitted to the intensive care unit due to asthma exacerbations.[2] Severe asthma is twice as common in individuals with N-ERD compared to the general asthma population. Asthma symptoms can be severe, and treatment is difficult. Aspirin therapy after desensitization (ATAD) and biological therapy are successfully used in many patients.[3] Upper respiratory tract symptoms are also severe, in addition to lower respiratory tract symptoms. The treatment of CRSwNP is difficult due to the high likelihood of NP being resistant to treatment and their common recurrence.[4-8] In a previous study, 80% of patients with

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NP who had N-ERD required revision surgery because ATAD had not been applied.[8]

In most patients with N-ERD, asthma symptoms emerge one to five years after upper respiratory tract symptoms, while NSAID hypersensitivity develops years later.[9,10] Relying solely on anamnesis may not be sufficient to diagnose N-ERD, and the gold standard diagnostic test is the aspirin provocation test.[11,12] The early diagnosis of N-ERD is essential for the successful management of the disease and allows patients' timely access to appropriate treatment. However, N-ERD often cannot be diagnosed early due to its variable clinical symptoms, a lack of validated *in vitro* tests and biomarkers, the long disease course, and low clinical suspicion. There is insufficient data in the literature regarding the extent and implications of diagnostic delays in N-ERD. Enhancing our understanding of N-ERD will facilitate early diagnosis and prompt the timely initiation of successful treatment.

This study aimed to provide a better understanding of the course of N-ERD, analyze whether there was a delay in clinical diagnosis, and explore the factors that might cause diagnostic delay.

MATERIAL AND METHODS

This observational, cross-sectional study was conducted at the Hacettepe University Faculty of Medicine, Adult Allergy and Immunology Clinic. It included patients aged 18 and older who were diagnosed with N-ERD from January 1, 2010, through December 27, 2023. Patients with asthma and recurrent nasal polyposis were diagnosed with N-ERD based on their history of multiple respiratory reactions occurring within 1-2 hours after NSAID intake, or positive results from an aspirin provocation test.[1] The patients' demographic characteristics, comorbidities, smoking status, medications used for N-ERD treatment, the use of biological therapy and ATAD, nasal polypectomy history, pulmonary function test parameters [forced expiratory volume in 1 (FEV1) second, forced vital capacity (FVC), and FEV1/FVC ratio] obtained at the time of clinician diagnosis, asthma control test (ACT) scores obtained at the time of clinician diagnosis, serum eosinophil count, serum total immunoglobulin (Ig) E level, skin prick test results, and food allergy history were recorded.

ACT is a test used to evaluate control of asthma symptoms. An ACT score below 20 points is a sign of uncontrolled asthma, while a score of 20-25 points indicates well-controlled asthma.[13]

The mean and median values of the time from the first symptom onset to the diagnosis of N-ERD, as well as the diagnosis times of asthma, CRSwNP, and NSAID hypersensitivity, were recorded. The mean and median values of the diagnosis times of asthma + CRSwNP, asthma + NSAID hypersensitivity, and CRSwNP + NSAID hypersensitivity were also calculated.

The suspected diagnosis was defined as when the patient exhibited two components of the N-ERD triad (asthma and CRSwNP, asthma and NSAID hypersensitivity; or CRSwNP and NSAID hypersensitivity). The time of clinician diagnosis was defined as the date when the triad (asthma, CRSwNP, NSAID hypersensitivity) was complete and the clinician officially diagnosed N-ERD. The actual diagnosis time was defined as the date when the patient completed the triad. The diagnostic latency period was defined as the time interval between the actual diagnosis and the clinician diagnosis. If the duration between the actual diagnosis time and the time of receiving the N-ERD diagnosis exceeds 6 months, this is defined as diagnostic delay. In other words, a diagnostic latency period of more than 6 months, was defined as diagnostic delay (Figure 1). The patients were divided into two groups according to whether they had a diagnostic delay. Statistical analyses were performed to determine the parameters that potentially caused this delay.

The study was approved by the Ethics Committee of Hacettepe University Hospital (approval number: 24/239, date: 02.04.2024). The recommendations of the World Medical Association Declaration of Helsinki were followed.

Statistical Analysis

IBM Statistical Package for Social Sciences v. 11.5 was used for the statistical analysis of the data. The results were presented with cross-tabulations and evaluated with the Pearson chi-square analysis. For 2x2 tables that had more than 25% of cells with expected values below 5, Fisher's exact test was employed. To determine the statistical analysis method to be used for the comparison of laboratory values according to the diagnostic delay status, the Kolmogorov-Smirnov and Shapiro-Wilks tests

Main Points

- High prevalence of diagnostic delay: The study found that 36.4% of patients with non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) experienced a significant diagnostic delay, averaging seven years. This delay was observed more frequently in female patients.
- Lack of association with common risk factors: No significant relationship was detected between the delay in N-ERD diagnosis and factors such as age, sex, allergy status, smoking, comorbidities, or total IgE and eosinophil levels. However, thyroid dysfunction was more prevalent among patients with delayed diagnosis.
- Chronic rhinosinusitis as the initial symptom: Most patients first developed chronic rhinosinusitis, followed by asthma and finally NSAID hypersensitivity, indicating a progression of symptoms over time.
- The need for early diagnosis and intervention: The study emphasizes the importance of early diagnosis of N-ERD to allow timely initiation of treatment. Delays in diagnosing NSAID hypersensitivity can result in more severe disease progression and complications, such as increased asthma exacerbations and frequent nasal polyp recurrence.
- Raising awareness among non-allergist physicians: The delay in diagnosis may be attributed to low awareness of N-ERD among non-allergist physicians and the lack of routine aspirin challenge testing. The study calls for improved awareness and the availability of standardized diagnostic protocols to facilitate early identification and management of N-ERD.

were applied to the dataset to investigate the normality of the data distribution. Additionally, the homogeneity of variances was examined with the Levene test. Since the data did not meet the parametric distribution assumptions, the Mann-Whitney U test was used. Within the scope of the analysis, results with a *P* value of <0.05 were considered statistically significant.

RESULTS

A total of 107 patients diagnosed with N-ERD were included in the study. The mean age of the patients was 45.84±12.1 [interquartile range (IQR): 20-70] years, and 38 (35.5%) of the patients were male. The mean serum eosinophil count at the time of clinician diagnosis was 514.4±401.8 (IQR: 215.0-700.0) cells/mm^3, and total IgE was 210.8±268.7 (IQR: 61.0-238.0) UI/mL. The mean ACT score was 19.5±5 (IQR: 15.3-24.0). Nasal polypectomy operations had been performed three or more times in 46 (43.0%) patients; 16 times in one (0.93%) patient; 11 times in two (1.8%) patients; and 10 times in four (3.7%) patients. Of the patients, 19 (17.8%) were sensitized to house dust mite, and 15 (14%) to pollen. Twenty (19.4%) patients were active smokers. The general characteristics of the patients are presented in Table 1 according to the presence of diagnostic delay.

Forty-seven (43.9%), patients with a strong clinical history of N-ERD were diagnosed solely based on their clinical history, without the need for an aspirin challenge test. Sixty (56.1%) patients underwent aspirin challenge testing, which confirmed the diagnosis of N-ERD. Thirty-nine (36.4%) patients had a delayed diagnosis. The mean diagnostic delay time for N-ERD was 7.4±6.6 (IQR: 2.0-12.0) years. The delay in diagnosis was not related to age (*P* = 0.514), sex (*P* = 0.878), allergy status (*P* = 0.137), smoking status (*P* = 0.148), eosinophil count at the time of clinician diagnosis (*P* = 0.316), total IgE (*P* = 0.919), and ACT score (*P* = 0.147). In addition, thyroid dysfunction was observed more frequently in the group with diagnostic delay (*P* = 0.021) (Table 1). Thyroid dysfunction was observed in 10 (9.35%) of the subjects. Among these, 7 (17.95%) were in the group with diagnostic delay, 6 (85.7%) were diagnosed with Hashimoto's thyroiditis, 5 (71.4%) presented with hypothyroidism, and 1 (14.3%) with hyperthyroidism. The patients had been diagnosed with CRSwNP, asthma, and NSAID hypersensitivity for an average duration of 14.9±9.6, 14.3±9.9, and 11.7±9.3 years, respectively. In the group without diagnostic delay, the mean duration of NSAID hypersensitivity was 9.6±8.4 (IQR: 3.0-15.0) years, and the mean duration of NSAID hypersensitivity + asthma was 9.1±7.4 (IQR: 3.0-14.0) years. According to the paired evaluation, the time since diagnosis was 12.9±9.3 (IQR: 5.0-20.0) years for the patients with asthma + CRSwNP, 10.3±7.8 (IQR: 4.0-15.0) years for those with asthma + NSAID hypersensitivity, and 10.6±7.9 (IQR: 4.0-16.0) years for those with CRSwNP + NSAID hypersensitivity (Table 2). N-ERD developed 2.9±5.0 years on average (IQR: 0.0-27.0) after the diagnosis of asthma and CRSwNP, and there was no significant difference between the groups with and without delay in diagnosis (*P* = 0.06).

At the time of inclusion into the study, the mean time elapsed since the clinician's N-ERD diagnosis was 7.1±6.9 (IQR: 1.0-10.0) years. If there had not been a diagnostic delay, the disease would have been diagnosed on average 9.8±7.8 (IQR: 3.0-15.0) years earlier. The mean time from the onset of symptoms for the first component of the N-ERD triad to the N-ERD diagnosis was 9.7±8.9 years (IQR: 2.0-15.7), and the mean time to actual diagnosis was 7.0±7.9 (IQR: 2.0-9.9) years (Table 3).

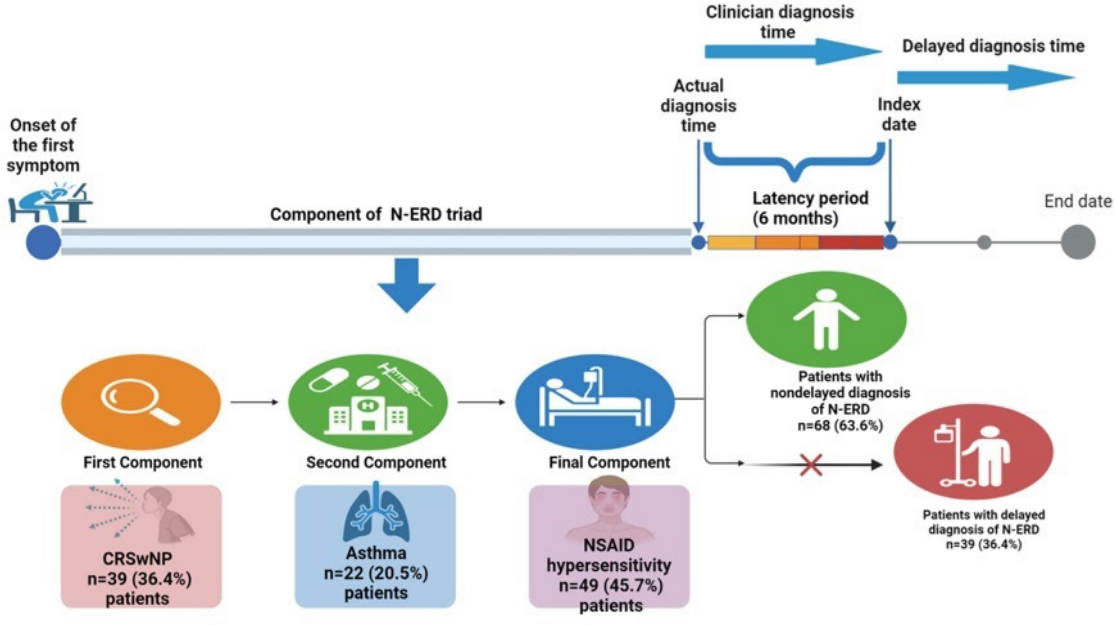

Figure 1. Visual summary

NSAID: non-steroidal anti-inflammatory drug, CRSwNP: chronic rhinosinusitis with nasal polyps, N-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease

Table 1. Characteristics of the patients according to the presence of a delay in N-ERD diagnosis

	Total (n = 107)	Diagnostic delay		
		Present (n = 39)	Absent (n = 68)	*P*
Age (year), mean±SD (median; IQR)	45.84±12.1 (46.0; 36.0-46.0)	48.5±11.7 (50.0; 40.0-57.0)	44.3±12.4 (42.0; 33.3-53.0)	0.070
Sex, n (%)				0.950
Female	69 (64.5)	25 (36.2)	44 (63.8)	
Male	38 (35.5)	14 (36.9)	24 (63.1)	
Comorbidity, n (%)				
Hypertension				0.814
Absent	89 (83.2)	32 (36.0)	57 (64.0)	
Present	18 (16.8)	7 (38.9)	11 (61.1)	
Diabetes mellitus				0.484
Absent	99 (92.5)	37 (37.3)	62 (62.7)	
Present	8 (7.5)	2 (25.0)	6 (75.0)	
Thyroid dysfunction				0.021*
Absent	97 (90.7)	32 (33.0)	65 (67.0)	
Present	10 (9.3)	7 (70.0)	3 (30.0)	
Coronary artery disease				0.463
Absent	103 (96.3)	37 (35.9)	66 (64.1)	
Present	4 (3.7)	2 (50.0)	2 (50.0)	
Malignancy				0381
Absent	101 (94.4)	36 (35.7)	65 (64.3)	
Present	6 (5.6)	3 (50.0)	3 (50.0)	
Smoking tobacco use, n (%)				0.168
Current	20 (19.4)	4 (20.0)	16 (80.0)	
Never	60 (58.3)	26 (43.3)	34 (56.7)	
Former	23 (22.3)	8 (34.8)	15 (65.2)	
Asthma inhaler treatment, n (%)				
ICS	21 (19.6)	6 (28.6)	15 (71.4)	-†
SABA	3 (2.8)	1 (33.3)	2 (66.7)	
ICS + LABA	63 (58.9)	26 (41.3)	37 (58.7)	
ICS + LABA + LAMA	9 (8.4)	2 (22.2)	7 (77.8)	
ICS + LABA + SABA	11 (10.3)	4 (36.3)	7 (63.7)	
ATAD, n (%)	54 (50.5)	18 (33.3)	36 (66.7)	
Absent	53 (49.5)	21 (39.6)	32 (60.4)	-†
100 mg	4 (3.7)	2 (50.0)	2 (50.0)	
300 mg	45 (42.1)	18 (40.0)	27 (60.0)	
500 mg	1 (0.9)	0 (0.0)	1 (100.0)	
600 mg	3 (2.8)	1 (33.3)	2 (66.7)	
Biological therapy, n (%)				0.915
Absent	82 (76.6)	29 (35.4)	53 (64.6)	
Mepolizumab	15 (14.0)	6 (40.0)	9 (60.0)	
Omalizumab	10 (9.3)	4 (40.0)	6 (60.0)	
Nasal polyp operation, n (%)				0.292
None	19 (17.8)	4 (21.0)	15 (79.0)	

Table 1. Continued

	Total (n = 107)	Diagnostic delay		
		Present (n = 39)	Absent (n = 68)	*P*
<3	42 (39.3)	16 (38.1)	26 (61.9)	
≥3	46 (43.0)	19 (41.3)	27 (58.7)	
Food allergy, n (%)				
Present	17 (15.9)	5 (29.4)	12 (70.6)	0.511
Absent	90 (84.1)	34 (37.8)	56 (62.2)	
Pollen allergy, n (%)				
Present	15 (14.0)	8 (53.3)	7 (46.7)	0.143
Absent	92 (86.0)	31 (33.7)	61 (66.3)	
House dust mite allergy, n (%)				
Present	19 (17.8)	4 (21.1)	15 (78.9)	0.124
Absent	88 (82.2)	35 (39.7)	53 (60.3)	
PFT				
FEV1, mean±SD (median; IQR)	82.1±17.0 (84.0; 74.5-95.5)	79.7±15.6 (82.0; 66.0-90.0)	83.5±17.7 (84.0; 75.0-98.0)	0.317
ACT, mean±SD (median; IQR)	19.5±5 (22.0; 15.3-24.0)	20.6±4.8 (22.0; 17.5-24.3)	18.8±5.0 (20.0; 14.0-22.0)	0.051
Serum total IgE level (UI/mL), mean±SD (median; IQR)	210.8±268.7 (113.0; 61.0-238.0)	204.0±205.2 (169.0; 66.5-260.5)	215.0±302.9 (102.0; 61.0-231.8)	0.513
Serum eosinophil count (cells/mm³), mean±SD (median; IQR)	514.4±401.8 (400.0; 215.0-700.0)	468.2±310.8 (400.0; 300.0-600.0)	541.7±447.0 (450.0; 200.0-700.0)	0.711

*$P < 0.05$; †statistical value could not be calculated because the number of cells with expected values below 5 was more than 25%.

SD: standard deviation, IQR: interquartile range, ICS: inhaler corticosteroid, LABA: long-acting ß2-agonist, LAMA: long-acting muscarinic antagonist, SABA: short-acting ß2 agonist, ATAD: aspirin therapy after desensitization, PFT: pulmonary function test, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, ACT: asthma control test, IgE: immunoglobulin E

Table 2. Relationship between the time since disease diagnosis and delay in N-ERD diagnosis

Time since diagnosis (year), mean±SD (median; IQR)	Total (n = 107)	Diagnostic delay	
		Present (n = 39)	Absent (n = 68)
Asthma	14.3±9.9 (13.0; 7.0-22.0)	16.1±7.9 (15.0; 10.0-22.0)	13.3±10.8 (9.5; 4.3-22.0)
NSAID hypersensitivity	11.7±9.3 (10.0; 5.0-16.0)	15.4±9.7 (16.0; 8.0-20.0)	9.6±8.4 (8.5; 3.0-15.0)
CRSwNP	14.9±9.6 (15.0; 7.0-22.0)	17.4±8.4 (18.0; 10.0-22.0)	13.5±9.9 (11.5; 6.0-20.0)
Asthma + NSAID hypersensitivity (suspected diagnosis)	10.3±7.8 (9.0; 4.0-15.0)	13.5±7.4 (14.0; 7.0-18.0)	8.5±7.4 (6.5; 3.0-13.0)
Asthma + CRSwNP (suspected diagnosis)	12.9±9.3 (11.0; 5.0-20.0)	14.9±7.9 (14.0; 9.0-22.0)	11.6±9.7 (9.0; 3.0-20.0)
NSAID hypersensitivity + CRSwNP (suspected diagnosis)	10.6±7.9 (9.0; 4.0-16.0)	13.9±8.1 (14.0; 7.0-20.0)	8.7±7.2 (8.0; 3.0-14.5)

SD: standard deviation, IQR: interquartile range, NSAID: non-steroidal anti-inflammatory drug, CRSwNP: chronic rhinosinusitis with nasal polyps, N-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease

Table 3. Time from symptom onset to the diagnosis of N-ERD and actual and N-ERD diagnosis times according to the presence of diagnostic delay

	Total (n = 107)	Diagnostic delay	
		Present (n = 39)	Absent (n = 68)
Time since actual diagnosis (year)	9.8±7.8 (9.0; 3.0-15.0)	12.6±7.9 (11.0; 5.0-18.0)	8.2±7.3 (6.0; 3.0-11.0)
Time since N-ERD diagnosis (year)	7.1±6.9 (4.0; 1.0-10.0)	5.2±5.7 (3.0; 1.0-9.0)	8.1±7.3 (6.0; 3.0-11.0)
Time from symptom onset to actual diagnosis (year)	7.0±7.9 (5.0; 2.0-9.9)	6.5±7.8 (5.0; 3.0-7.0)	7.3±8.1 (5.0; 1.3-10.0)
Time from symptom onset to N-ERD clinician diagnosis (year)	9.7±8.9 (8.0; 2.0-15.7)	13.8±8.9 (12.0; 7.0-18.0)	7.3±8.0 (5.0; 1.3-10.0)

Data presented as mean±standard deviation (median; interquartile range).
N-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease

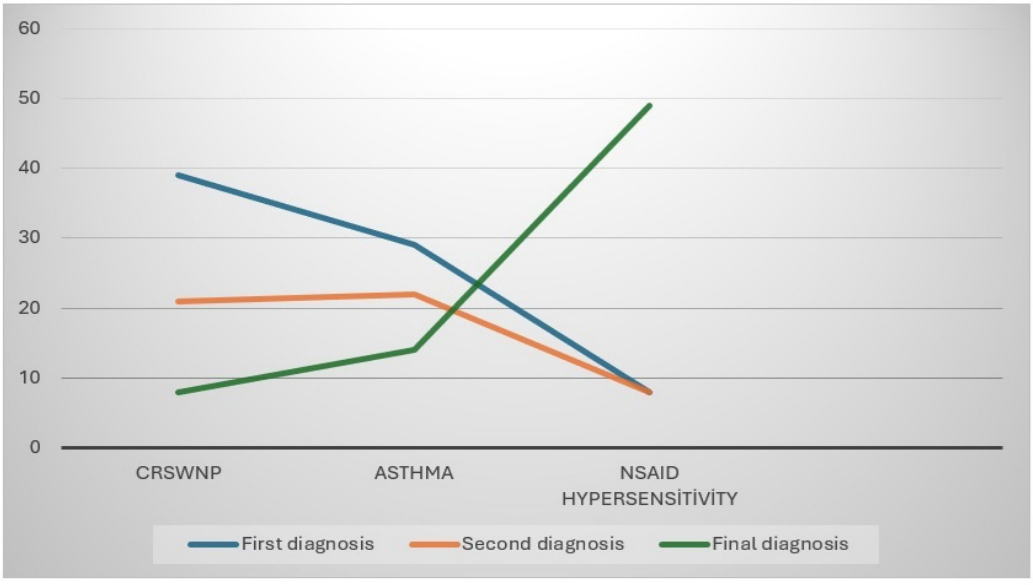

Figure 2. Chronological order of the N-ERD triad

NSAID: non-steroidal anti-inflammatory drug, CRSwNP: chronic rhinosinusitis with nasal polyps, N-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease

Of the patients in the group with diagnostic delay, 25 (64.1%) were female, and 14 (35.9%) were male. The mean age at which women received their first N-ERD diagnosis was 39.3±12.2 (IQR: 11.0-65.0) years, whereas this value was 38.2±10.4 (IQR: 19.0-65.0) years for men, with no significant difference found between the two (P = 0.774). The mean age at which the first symptoms began was 28.6±10.5 (IQR: 4.0-58.0) years, and there was no significant difference according to sex (P = 0.332).

Chronologically, the first diagnosis was CRSwNP in 39 (36.4%) patients, asthma in 29 (27.1%), asthma + CRSwNP in 19 (17.7%), and NSAID hypersensitivity in eight (7.4%). The second diagnosis was asthma in 22 (20.5%) patients, CRSwNP in 21 (19.6%), and NSAID hypersensitivity in eight (7.4%). The final diagnosis was NSAID hypersensitivity in 49 (45.7%) patients, asthma in 14 (13.0%), CRSwNP in eight (7.4%), simultaneous asthma + NSAID hypersensitivity following the CRSwNP diagnosis in 12 (11.7%), simultaneous CRSwNP + NSAID hypersensitivity following the asthma diagnosis in 11 (10.2%), and simultaneous asthma + CRSwNP following the NSAID hypersensitivity diagnosis in two (1.8%) (Figure 2). The remaining 10 (10.2%) patients were diagnosed with CRSwNP, asthma, and NSAID hypersensitivity simultaneously.

DISCUSSION

In our study, we found that 36.4% of patients diagnosed with N-ERD experienced an average diagnosis delay of seven years, and this was observed more frequently in women (64.1%). Consistent with previous reports, we determined that N-ERD usually started in the third or fourth decade of life and had a higher prevalence among women. The mean age at the diagnosis of N-ERD was previously reported to be 46 years by Roland et al.[14] and 30 years by Szczeklik et al.[9]

In a study undertaken by Kshirsagar et al.,[15] 24.4% of patients diagnosed with N-ERD had a diagnosis delay of one year or more from the onset of symptoms, and patients with allergies were found to be diagnosed earlier. The authors explained this finding by suggesting that patients with allergies possibly consult specialists more frequently. However, no relationship was detected between diagnostic delay and various factors, including age, sex, race, obesity, alcohol consumption, tobacco use, diabetes mellitus, and sleep apnea. In contrast, we did not find any relationship between allergy status and diagnostic delay. This may be because they evaluated the allergy status of their patients based on the International Classification of Diseases codes in their files, while we record allergies based on the findings from the anamnesis, skin prick tests, and specific IgE blood test results. Similar to the study by Kshirsagar et al.,[15] we determined that age, sex, smoking, comorbidities, number of nasal polypectomies, and treatment methods used were not risk factors for delayed diagnosis of N-ERD. Furthermore, we observed that the total IgE and eosinophil levels of the patients in the group without diagnostic delay were slightly higher, although the difference did not reach statistical significance. This may also be the reason why patients are referred to allergists in a timely manner. Our study additionally revealed that individuals with a diagnostic delay had a higher prevalence of thyroid dysfunction among comorbidities. Among the comorbidities observed in our study, thyroid dysfunction, particularly hypothyroidism and Hashimoto's thyroiditis, was found to be more common in patients with delayed N-ERD diagnoses. This observation aligns with previous studies reporting a higher prevalence of Hashimoto's thyroiditis in women, especially those with non-allergic asthma.[16] Thyroid dysfunction, including hypothyroidism and hyperthyroidism, can present with respiratory manifestations such as respiratory muscle weakness, upper airway obstruction, and dyspnea. These symptoms may obscure or mimic the clinical presentation of N-ERD, complicating the diagnostic process.[17-19]

The majority of patients with N-ERD first develop chronic rhinosinusitis, followed by asthma, and then aspirin or NSAID sensitivity, conditions that gradually progress over years.[10] In a previous study, Szczeklik et al.[9] first detected rhinitis, then followed by asthma, aspirin intolerance, and nasal polyposis in their patients. In the current study, we found that upper respiratory tract symptoms appeared first, followed by asthma, and finally NSAID hypersensitivity. While some patients were diagnosed with NSAID hypersensitivity first (7.4%), others (11.2%) received all three diagnoses simultaneously. The literature contains research in which N-ERD phenotyping was performed on patients according to their clinician diagnoses,[20] but there is still a clear need for further studies to investigate the effect of the initial condition of patients on disease severity and progression to offer a better understanding of the heterogeneous structure of N-ERD.

A recent study found that the mean delay in diagnosis three years for patients who were unaware of NSAID hypersensitivity.[20] NSAID hypersensitivity may be underdiagnosed due to the lack of routine aspirin challenge testing in asthmatic patients who do not report a history of drug allergies. However, the delayed identification of NSAID hypersensitivity can have direct consequences for patients. Marquette et al.[2] reported that 25% of asthmatic patients diagnosed with N-ERD required urgent mechanical ventilation. In a recent study, patients with a delayed diagnosis of N-ERD were found to be more likely to receive two or more courses of systemic steroids.[20]

Berges-Gimeno et al.[10] determined that N-ERD developed in patients within an average of 13 years from the onset of the first symptom. In our study, N-ERD developed within an average of seven years from the onset of the first symptom. At the time of the emergence of the first symptom, it may be difficult for clinicians to anticipate that a patient will develop N-ERD. In our study, patients with asthma and CRSwNP, having completed the N-ERD triad, were diagnosed with NSAID hypersensitivity after an average of three years. The diagnosis of N-ERD should be excluded by performing the aspirin challenge test in appropriate patients presenting with asthma and CRSwNP. Although clinicians may be hesitant due to potential reactions with the aspirin challenge test, studies have shown that it is a reliable method if performed under the supervision of qualified professionals according to defined protocols.[1] The emergence of a classification system encompassing all phenotypes, including incomplete and pseudoforms of N-ERD, is deemed crucial.[21,22] Moreover, early diagnosis can facilitate the consideration of treatment interventions such as ATAD and biological therapies, known for their effectiveness.

While raising awareness may reduce diagnostic delays, the retrospective nature of this study limits its scope, highlighting the need for future research.

CONCLUSION

While raising awareness may reduce diagnostic delays, the retrospective nature of this study limits its scope, highlighting the need for future research. Despite recent significant advances in understanding the pathomechanism of N-ERD, this study revealed that the diagnosis of patients was delayed in clinical practice. The observed delay in diagnosis may be attributed to the low awareness of N-ERD among non-allergist physicians, such as pulmonologists and otolaryngologists the physicians' reluctance to perform aspirin provocation tests, as well as the limited availability of these tests in all centers. The other reasons for delayed diagnosis could be patients' non-compliance and sociocultural or socioeconomic issues. Failure to initiate proper treatment in patients with N-ERD may lead to an increased frequency of asthma exacerbations, nasal polyp recurrence, additional surgery requirements, and severe NSAID hypersensitivity reactions.

Ethics

Ethics Committee Approval: The study protocol was approved by the Hacettepe University Hospital (approval number: 24/239, date: 02.04.2024).

Informed Consent: Retrospective study.

Presented in: This manuscript was previously presented as an oral presentation at the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2024 and the Turkish Thoracic Society Congress.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.C., H.K., Ç.T., Concept: M.C., E.D., G.K., A.F.K., Design: M.C., A.F.K., G.K., E.D., Data Collection or Processing: M.C., H.K., Ç.T., Analysis or Interpretation: M.C., H.K., Ç.T., Literature Search: M.C., H.K., Ç.T., Writing: M.C., E.D., G.K., A.F.K.

Conflict of Interest: Gül Karakaya has performed lectures or acted as an advisor for Novartis, GSK, AstraZeneca, Takeda, and Acino. Other authors declare no conflict of interest.

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