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*Research Article*

# Evaluation of Patch Test Results with the T.R.U.E. Test and Demographic Findings in Periorbital Dermatitis: A 10-Year Retrospective Analysis

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The most common cause of periorbital dermatitis is allergic contact dermatitis. This study aimed to determine the patch test results and demographic characteristics in patients diagnosed with periorbital dermatitis by evaluating their patch test results between 2012 and 2022. The thin-layer rapid-use epicutaneous test (T.R.U.E. test) results of patients diagnosed with periorbital dermatitis over the specified period were retrospectively evaluated. Of the 102 patients included in the study, 58 (56.9%) had a positive reaction to at least one allergen. The most common allergens to which the patients had positive reactions were nickel sulfate (31.0%), gold sodium thiosulfate (19.0%), fragrance mix (13.8%), balsam of Peru (10.3%), colophony (10.3%), cobalt dichloride (8.6%), formaldehyde resin (6.9%), thimerosal (5.2%), quaternium-15 (5.2%), carba mix (5.2%), and potassium dichromate (5.2%). This study provides comprehensive data on the demographic characteristics and patch test results of patients with periorbital dermatitis.

## 1. Introduction

The periorbital region is among the most common areas of allergic contact dermatitis (ACD) [1]. Due to the face and the scalp being the areas where cosmetic products are often used, periorbital dermatitis is frequently seen. Another reason for the high incidence of periorbital dermatitis is that the eyelid skin is very thin (0.55 mm, as opposed to 2 mm in the remaining facial skin), which causes both contact and airborne allergens to easily penetrate this area. Exposure to allergens on the fingertips due to their unprotected position and the frequent touching of the face with hands are among the other reasons that increase the frequency of contact dermatitis in the periorbital region [2].

Another important aspect of periorbital dermatitis is that many chronic skin diseases, including atopic dermatitis (AD), seborrheic dermatitis (SD), psoriasis, rosacea, cutaneous T-cell lymphoma, and dermatomyositis, are considered in the differential diagnosis of or associated with ACD [3]. Irritant contact dermatitis (ICD), airborne contact dermatitis (ABCD), urticaria, drug reactions, phototoxic dermatitis, blepharitis, and other infections are other diseases included in differential diagnosis [2, 3]. In periorbital dermatitis, identifying the causative allergen by making an early diagnosis will prevent serious side effects, such as cataracts and glaucoma, which may develop due to the chronic use of topical corticosteroids on the eyelids as the first-choice treatment [4]. Common allergens include aeroallergens (e.g., fragrances), direct contact (e.g., cosmetics and ophthalmic drugs), and ectopic exposures (e.g., nail polishes) [5]. The patch test is the gold standard diagnostic method for the diagnosis of ACD and the detection of allergens [1]. Genetics, geography, socioeconomic circumstances, age, atopy, and sex influence the allergens that cause contact sensitivity [6]. The emergence of new allergens over time can also affect the frequency of sensitivity to existing allergens. In the literature, there are studies reporting patch test results in periorbital dermatitis from many countries [3, 7–12]. Although there are studies reporting patch test results in patients with ACD in the Turkish population, no

study was found examining patch test results in periorbital dermatitis. Therefore, in this study, patients diagnosed with periorbital dermatitis between 2012 and 2022 were evaluated using the T.R.U.E. patch test to determine the frequency of sensitivity to the allergens included in this test. In addition, the results were compared to other populations, as reported in the literature, and the demographic characteristics and changes in the frequency of allergen sensitivity were examined over the years.

## 2. Materials and Methods

Between January 2012 and December 2022, 102 patients aged 18 years and over, who presented to the dermatology outpatient clinic of Istanbul Medipol University with complaints such as redness, itching, and scaling in the periorbital region and underwent the patch test with the suspicion of ACD, were included in the study. The patients' age, gender, disease duration, history of suspected allergen exposure, history of atopy (personal or familial allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and asthma), history of drug use, concomitant dermatological diseases (seborrheic dermatitis, atopic dermatitis, psoriasis, rosacea, urticaria, etc.), the presence of any additional body region with dermatitis, the date of presentation, profession, and the final diagnosis were retrospectively screened from the patient files and recorded. The study was approved by the Ethics Committee of Istanbul Medipol University, with decision number 1096.

In all patients, the thin-layer rapid-use epicutaneous test (T.R.U.E. test, SmartPractice Denmark, Hiller□d) was administered. For the three patients who presented in 2012, a T.R.U.E. test panel comprising 24 allergens and allergen mixtures was utilized, while for the remaining 99 patients, the 2012 formulation of the T.R.U.E. test, which includes 35 allergens (28 individual allergens and seven allergen mixes) and one negative control, was employed [13, 14]. The patch test was not performed on patients using systemic steroids or any other immunosuppressive medication. These drugs were discontinued at least one month before the test procedure. Topical steroids applied to the test area were discontinued at least seven days before the procedure. The patch test was adhered to a clean, dry, hairless, and lesion-free area on the upper back of the patients for two days (application day, day 0 (D0)). During this period, the patients were asked not to engage in any physical exercise or sweat. The patches remained in place for 48 hours. The first and second patch test readings were performed at 48 hours and 72–168 hours after the placement of the initial patches by a dermatologist. Reactions were assessed according to the International Contact Dermatitis Research Group criteria on D2, D3, or D4, and D7 and recorded as follows: no reaction, (−); only slight erythema, doubtful reaction; possible erythema, infiltration, and papules, (+); erythema, infiltration, papules, and vesicles, (++); and intense erythema, infiltration, confluent vesicles, and bullae, (+++) [15]. Reactions with a decrescendo pattern consisting of sharply defined, noninfiltrating erythema, follicular erythema, and sometimes hemorrhagic and follicular pustules were considered irritant reactions. Irritant, doubtful, and negative responses were recorded as negative. At least 1 + reaction was considered a positive patch test result [16]. The diagnosis of ACD was made based on a combination of clinical features (pruritic, eczematous eruption on the skin area where the contact allergen came into contact), a history of presumed allergen exposure, histopathological examination in necessary cases, and a positive patch test result. Patients who did not meet all these criteria were included in other appropriate diagnostic groups (ICD, AD, SD, ABCD, or others). The Hanifin–Rajka criteria were used for the diagnosis of atopic dermatitis [17].

All data were recorded, retrieved, and evaluated using a computer database. Cross-tabs and descriptive statistics were used in statistical analyses. Data analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics v. 26.0. A $p$ value of ≤0.05 was considered statistically significant.

## 3. Results

Of the 102 patients included in the sample over the 11-year period, 76 (74.5%) were female and 26 (25.5%) were male. The mean age was 35.6 (18–71) years. Seventy-two (70.6%) patients were 40 years or younger, and 30 (29.4%) were over 40. The mean disease duration was 8 (0.5–60) months. The patients' clinical and demographic data are shown in Table 1. When the demographic characteristics of the patients were evaluated according to the lesion localization, 37.5% of those with lesions in the periorbital region had a history of atopy, and the frequency of atopy history increased in those with the involvement of other body regions, as well as the periorbital region; however, no significant correlation was found ($p > 0.05$). When the presence of concomitant dermatological diseases was compared according to the lesion localization, it was determined that the frequency of atopic dermatitis in the patients with eyelid dermatitis accompanied by trunk involvement was significantly higher than that in those with only periorbital involvement ($p < 0.05$) (Table 2).

A positive reaction against at least one allergen was detected in 58 (56.9%) of the patients who underwent the patch test. 32 patients (31.3%) were positive for a single allergen and 26 patients (25.4%) for more than one allergen. Ninety-one positive reactions were detected in 58 patients. Among the positive reactions, a positive reaction of equal severity was found in 48 (52.7%) in readings at D2 and D3/D4, a positive reaction of decreasing severity from D2 to D3/D4 in 28 (30.7%), and a positive reaction of increasing severity from D2 to D3/D4 in 11 (12.1%). In addition, four patients (4.4%) had positivity only on D7. The most common allergen to which the patients had positive reactions was nickel sulfate (31.0%), followed by gold sodium thiosulfate (GST) (19.0%), fragrance mix (13.8%), balsam of Peru (Myroxylon pereirae) oil (10.3%), colophonium (10.3%), cobalt dichloride (8.6%), p-tert-Butylphenol formaldehyde resin (6.9%), thimerosal (5.2%), quaternium-15 (5.2%), carba mix (5.2%), and potassium dichromate (5.2%) (Table 3).

Table 1: Demographic characteristics of the patients who underwent the patch test with the suspicion of ACD on the eyelid.

| | *n* | % |
|---|---|---|
| Age | | |
| ≤40 years | 72 | 70.6 |
| >40 years | 30 | 29.4 |
| Gender | | |
| Male | 26 | 25.5 |
| Female | 76 | 74.5 |
| Atopy history | | |
| Absent | 57 | 55.9 |
| Present | 45 | 44.1 |
| Patch test result | | |
| Negative | 44 | 43.1 |
| At least one positive | 58 | 56.9 |
| Presentation period | | |
| First 5.5 years (January 2012–June 2017) | 32 | 31.4 |
| Second 5.5 years (July 2017–December 2022) | 70 | 68.6 |
| Localization | 56 | 54.9 |
| Only POD | 29 | 28.4 |
| POD + head-neck | 15 | 14.7 |
| POD + trunk | 11 | 10.8 |
| POD + hands | 5 | 4.9 |
| POD + arms | 3 | 2.9 |
| POD + legs | | |
| Final diagnosis | | |
| ACD | 43 | 42.2 |
| ICD | 19 | 18.6 |
| AD | 15 | 14.7 |
| Other (psoriasis, rosacea, etc.) | 9 | 8.8 |
| ACD + AD | 7 | 6.9 |
| ABCD | 5 | 4.9 |
| Seborrheic dermatitis | 4 | 3.9 |
| Occupation | | |
| Unemployed (housewife, student, or retired) | 50 | 49 |
| Laborer* | 12 | 11.8 |
| Not available | 12 | 11.8 |
| Office worker | 10 | 9.8 |
| Healthcare worker | 6 | 5.9 |
| Other | 6 | 5.9 |
| Teacher | 3 | 2.9 |
| Flight personnel | 3 | 2.9 |

ACD, allergic contact dermatitis; POD, periorbital dermatitis; ICD, irritant contact dermatitis; AD, atopic dermatitis, *includes one hairdresser, three textile workers, two carpenters, one courier, one construction worker, and four laborers from other sectors.

Concerning the relationship of allergens with age, the rate of fragrance mix positivity in patch testing was higher over the age of 40 years, while positivity to balsam of Peru oil, colophonium, cobalt dichloride, and formaldehyde resin was relatively more common among those under 40. However, since the $p$ value was 0.312 ($p > 0.05$), there was no significant relationship between age and allergens. In order to evaluate changes in the frequencies of sensitivity to allergens over the study period, the data were compared between the first 5.5 and second 5.5 years. Although there was an increase in the frequency of positivity to nickel sulfate, GST, and colophony in the post-2017 period, no significant difference was found in terms of positivity frequencies in patch testing ($p > 0.05$) (Table 4).

Atopic patients were divided into two groups as follows: those with atopic dermatitis and those without atopic dermatitis. The positive patch test rates against at least one allergen in the patch test were compared between these groups. The rate of positivity for at least one allergen was 40.9% in the group with atopic dermatitis and 65.2% in the group without atopic dermatitis. No statistically significant difference was detected between the two groups ($p = 0.102$ and $p > 0.05$).

According to the final diagnoses of the patients based on the patch test results, a suspected allergen exposure history, drug use, accompanying dermatological diagnoses, and examination findings, the most common diagnosis was ACD (49.1%), followed by AD (21.6%), ICD (18.6%), other diseases (8.8%), ABCD (4.9%), and SD (3.9%). The total percentage exceeded 100% because some patients had more than one clinical diagnosis (Figure 1). Table 5 presents the relationship between possible clinical contactants of patients and allergens that were found positive in the patch test of the patients diagnosed with ACD and ABCD.

## 4. Discussion

Periorbital dermatitis is a clinical picture presenting with symptoms and signs, such as redness, dandruff, edema, itching, burning, and stinging on the eyelids and sometimes in the periorbital region. It may develop due to ICD or ACD or present as a clinical finding of AD, ABCD, SD, rosacea, or periorificial dermatitis [2, 3]. Almost all studies on the etiology of periorbital dermatitis suggest that ACD is the most common cause (32–77%) [7–12]. Frequencies of other causes vary between studies. In a study I conducted in 2023, evaluating the test results of 1,012 patients who underwent patch testing with a preliminary diagnosis of ACD at our clinic, I found that the most common area where dermatitis was detected was the hands (34.9%), followed by the head and neck region (22.2%). In that study, I reported that the highest rate of patch test positivity was detected in head and neck dermatitis, with the most commonly affected area being the periorbital region [6]. These results indicated the need for more detailed and extensive studies on periorbital dermatitis with frequent clinical involvement and high sensitivity rates. Consistent with my previous work and other publications in the literature; in the current study, ACD was found to be the most common final diagnosis with a frequency of 49.1%, followed by AD (21.6%), ICD (18.6%), other diseases (8.8%), ABCD (4.9%), and SD (3.9%). However, as is known, the importance of a positive patch test in the diagnosis of ACD is determined by examining the patient's clinical symptoms and history. The most reliable way to determine the clinical relevance of a positive patch test is to observe the regression of dermatitis by avoiding the allergens identified as positive. There is still no consensus on the definition, scoring, and determination of clinical relevance [18]. In the current study, the final diagnoses of the patients were determined retrospectively by reviewing the T.R.U.E. test results from patient records and histories of possible allergen exposure. Prospective studies should be conducted to determine the clinical relevance of patch test reactions and the frequency of ACD in periorbital

Table 2: Demographic characteristics of the patients according to the lesion localization.

| | Only POD | Hands | Arms | Legs | Trunk | Head-neck | *P* value |
|---|---|---|---|---|---|---|---|
| Total number | 56 | 11 | 5 | 3 | 15 | 29 | |
| Gender, *n* (%) | | | | | | | 0.151 |
| Male | 18 (32.1) | 2 (18.2) | — | 1 (33.3) | 2 (13.3) | 4 (13.8) | NS |
| Female | 38 (67.9) | 9 (81.8) | 5 (100.0) | 2 (66.7) | 13 (86.7) | 25 (86.2) | NS |
| Atopy, *n* (%) | | | | | | | 0.055 |
| Absent | 35 (62.5) | 4 (36.4) | 2 (40.0) | — | 5 (33.3) | 17 (58.6) | NS |
| Present | 21 (37.5) | 7 (63.6) | 3 (60.0) | 3 (100.0) | 10 (66.7) | 12 (41.4) | NS |
| Accompanying disease, *n* (%) | | | | | | | 0.000* |
| None | 40 (71.4) | 4 (36.4) | 2 (40.0) | 1 (33.3) | 5 (33.3) | 14 (48.3) | NS |
| AD | 9 (16.1) | 5 (45.5) | 3 (60.0) | 2 (66.7) | 9 (60.0)* | 8 (27.6) | 0.008 |
| SD | 6 (10.7) | 1 (9.1) | — | — | 1 (6.7) | 5 (17.2) | NS |
| Rosacea | — | — | — | — | — | 4 (13.8) | NS |
| Psoriasis | 1 (1.8) | 1 (9.1) | — | — | — | — | NS |
| Disease duration (mean) | 6.8 | 11.5 | 9.8 | 7.0 | 6.5 | 10.1 | — |
| Age (mean) | 37.2 | 31.8 | 31.6 | 36.3 | 31.1 | 31.8 | — |

*Note.* *Statistically significant at 0.05. NS, not significant; AD, atopic dermatitis; SD, seborrheic dermatitis.

Table 3: Distribution and concentration of allergens.

| | Dose/concentration | Number (percentage) of patients (total = 58) |
|---|---|---|
| Nickel sulfate | 200 mcg/cm$^2$ | 18 (31.0%) |
| Gold sodium thiosulfate | 75 mcg/cm$^2$ | 11 (19.0%) |
| Fragrance mix | 500 mcg/cm$^2$ | 8 (13.8%) |
| Balsam of Peru (myroxylon pereirae) oil | 800 mcg/cm$^2$ | 6 (10.3%) |
| Colophonium | 1,200 mcg/cm$^2$ | 6 (10.3%) |
| Cobalt dichloride | 20 mcg/cm2 | 5 (8.6%) |
| p-tert-Butylphenol formaldehyde | 45 mg/cm2 | 4 (6.9%) |
| Thimerosal | 7 mcg/cm$^2$ | 3 (5.2%) |
| Quaternium-15 | 100 mcg/cm$^2$ | 3 (5.2%) |
| Carba mix | 250 mcg/cm$^2$ | 3 (5.2%) |
| Potassium dichromate/Chromium | 54 mcg/cm$^2$ | 3 (5.2%) |
| Formaldehyde | 180 mcg/cm$^2$ | 2 (3.4%) |
| Cl+ Me-isothiazolinone (MCI/MI) | 4 mcg/cm$^2$ | 2 (3.4%) |
| Black rubber mix | 75 mcg/cm$^2$ | 2 (3.4%) |
| Epoxy resin | 50 mcg/cm$^2$ | 2 (3.4%) |
| Lanolin alcohols | 1,000 mcg/cm$^2$ | 2 (3.4%) |
| Bronopol | 250 mcg/cm$^2$ | 1 (1.7%) |
| Disperse blue 106 | 50 mcg/cm$^2$ | 1 (1.7%) |
| Parthenolide | 3 mcg/cm$^2$ | 1 (1.7%) |
| Mercaptobenzothiazole | 75 mcg/cm$^2$ | 1 (1.7%) |
| Hydrocortizone-17-butyrate | 20 mcg/cm$^2$ | 1 (1.7%) |
| Budesonide | 1 mcg/cm$^2$ | 1 (1.7%) |
| Quinoline mix | 190 mcg/cm$^2$ | 1 (1.7%) |
| Thiuram mix | 27 mcg/cm$^2$ | 1 (1.7%) |
| p-Phenylenediamine | 90 mcg/cm$^2$ | 1 (1.7%) |
| Paraben mix | 1,000 mcg/cm$^2$ | 1 (1.7%) |
| Caine mix | 630 mcg/cm$^2$ | 1 (1.7%) |

dermatitis. In our study, 10.8% ($n = 11$) of the patients were diagnosed with SD, of whom seven also had positive patch test results and a history of exposure to positive allergens. This result shows the importance of performing the patch test in patients with periorbital dermatitis accompanied by SD in order not to overlook a secondary diagnosis of ACD. The different frequencies reported for the cause of periorbital dermatitis in previous studies can be attributed to genetic and environmental differences between the evaluated populations.

Although periorbital dermatitis is seen in both genders, studies have reported that it is more common in women [7–12]. The use of cosmetics being much higher in women explains the higher frequency of this disease in this gender. Consistent with the literature, in the current study, 74.5% of the patients were female.

Metals (e.g., nickel sulfate, GST, and cobalt chloride), cosmetics (e.g., fragrance mix, balsam of Peru oil, methylisothiazolinone (MI), and acrylates), antibiotics (e.g., neomycin and bacitracin), and condoms (e.g., thiomersal) have

Table 4: Comparison of allergen positivity frequencies between the first and second 5.5 years of the study period.

| | Second half $n = 41$ | First half $n = 17$ | Total $n = 58$ | $P$ value |
|---|---|---|---|---|
| Nickel sulfate | 14 (34.1) | 4 (23.5) | 18 (31.0) | NS |
| Gold sodium thiosulfate | 10 (24.4) | 1 (5.9) | 11 (19.0) | NS |
| Fragrance mix | 5 (12.2) | 3 (17.6) | 8 (13.8) | NS |
| Balsam of Peru (myroxylon pereirae) oil | 4 (9.8) | 2 (11.8) | 6 (10.3) | NS |
| Colophonium | 5 (12.2) | 1 (5.9) | 6 (10.3) | NS |
| Cobalt dichloride | 3 (7.3) | 2 (11.8) | 5 (8.6) | NS |
| P-tert-Butylphenol formaldehyde | 3 (7.3) | 1 (5.9) | 4 (6.9) | NS |
| Thimerosal | 2 (4.9) | 1 (5.9) | 3 (5.2) | NS |
| Quaternium-15 | 1 (2.4) | 2 (11.8) | 3 (5.2) | NS |
| Carba mix | 1 (2.4) | 2 (11.8) | 3 (5.2) | NS |
| Potassium dichromate | 1 (2.4) | 2 (11.8) | 3 (5.2) | NS |
| Formaldehyde | 2 (4.9) | — | 2 (3.4) | NS |
| Cl+ Me-isothiazolinone (MCI/MI) | 2 (4.9) | — | 2 (3.4) | NS |
| Black rubber mix | 1 (2.4) | 1 (5.9) | 2 (3.4) | NS |
| Epoxy resin | 2 (4.9) | — | 2 (3.4) | NS |
| Lanolin alcohols | 1 (2.4) | 1 (5.9) | 2 (3.4) | NS |
| Bronopol | 1 (2.4) | — | 1 (1.7) | NS |
| Disperse blue 106 | 1 (2.4) | — | 1 (1.7) | NS |
| Parthenolide | — | 1 (5.9) | 1 (1.7) | NS |
| Mercaptobenzothiazole | 1 (2.4) | — | 1 (1.7) | NS |
| Hydrocortizone-17-butyrate | 1 (2.4) | — | 1 (1.7) | NS |
| Budesonide | — | 1 (5.9) | 1 (1.7) | NS |
| Quinoline mix | 1 (2.4) | — | 1 (1.7) | NS |
| Thiuram mix | — | 1 (5.9) | 1 (1.7) | NS |
| P-Phenylenediamine | 1 (2.4) | — | 1 (1.7) | NS |
| Paraben mix | — | 1 (5.9) | 1 (1.7) | NS |
| Caine mix | 1 (2.4) | — | 1 (1.7) | NS |
| Total | 41 (100.0) | 17 (100.0) | 58 (100.0) | |

NS, not significant, Note: *statistically significant at 0.05.

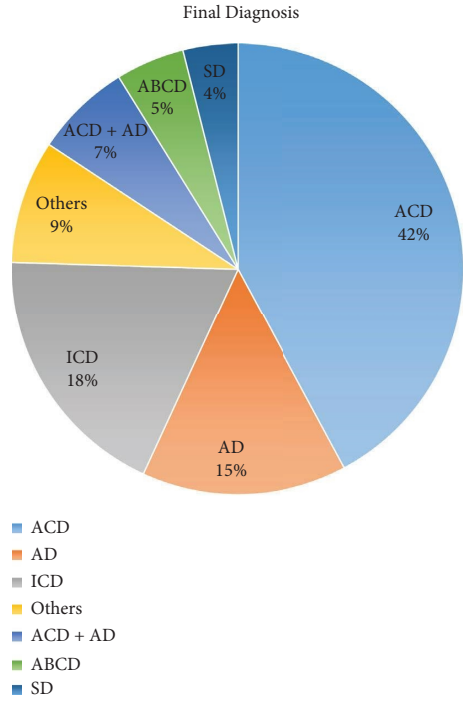


Figure 1: Final diagnoses of the patients (ACD: allergic contact dermatitis; AD: atopic dermatitis; ICD: irritant contact dermatitis; ABCD: airbone contact dermatitis; SD: seborrheic dermatitis).

Table 5: Relationship between possible clinical contactants and positive allergens in patch testing in patients diagnosed with allergic contact dermatitis and airborne contact dermatitis.

| Patient no | Gender | Age | Occupation | Positive allergens | Possible clinical contactants of patients |
|---|---|---|---|---|---|
| 1 | M | 40 | Tradesman | Fragrance mix | Presented in the label of the aftershave used |
| 2 | F | 34 | Housewife | Nickel sulphate | Presented in the label of the eye cosmetics used |
| 3 | M | 48 | Office worker | Lanolin alcohol | Presented in the label of the hair spray used (aeroallergen) |
| 4 | M | 45 | NA | Nickel sulphate | Started with the use of metal frame glasses |
| 5 | F | 45 | Housewife | Nickel sulphate*, GST | Occurs after using metal tweezers |
| 6 | F | 50 | Retired | Parthenolide | Presented in the label of the moisturizer used |
| 7 | F | 33 | NA | Nickel sulphate*, colophonium* | Presented in the label of the eyeliner, mascara, and other cosmetics used |
| 8 | F | 19 | Student | Formaldehyde resin | Presented in the label of the nail polish used (ectopic exposure) |
| 9 | F | 39 | Housewife | Thiomersal*, thiuram mix | Presented in the label of the contact lens solution used |
| 10 | F | 32 | Hairdresser** | Colophonium | Presented in the label of the eye cosmetics and pine gum used personally and occupationally |
| 11 | F | 24 | Housewife | Fragrance mix | Presented in the label of the shampoo used |
| 12 | F | 40 | Doctor | Nickel sulphate | Presented in the label of the mascara and eye cosmetics used |
| 13 | M | 41 | Construction worker** | Epoxy resin*, thiomersal | Presented in the label of the adhesives, floor coating, and varnishes occupationally used (aeroallergen) |
| 14 | F | 63 | Housewife | Fragrance mix | Presented in the label of the makeup remover and detergent used |
| 15 | M | 42 | NA | Nickel sulphate*, balsam of Peru | Started with the use of metal frame glasses |
| 16 | F | 32 | Housewife | Nickel sulphate | Presented in the label of the eyelash curler and mascara used |
| 17 | M | 48 | NA | Fragrance mix*, quaternium 15 | Presented in the label of the shampoo used |
| 18 | F | 25 | Housewife | Nickel sulphate | Presented in the label of the eye cosmetics used |
| 19 | M | 51 | Auto mechanic** | Potassium dichromate, carba mix* | Presented in the label of the car tires exposed and gloves and hoses used occupationally (ectopic exposure) |
| 20 | F | 41 | NA | Formaldehyde resin*, gold sodium thiosulphate | Presented in the label of the nail polish used (ectopic exposure) |
| 21 | F | 44 | Housewife | Quaternium 15 | Presented in the label of the sunscreen used |
| 22 | F | 31 | Flight attendant | Balsam of Peru, gold sodium thiosulphate* | Presented in the label of the eye cosmetics and jewelry used |
| 23 | F | 54 | Retired | Fragrance mix, formaldehyde* | Presented in the label of the fabric paint and adhesives used in hobby-related activities (ectopic exposure) |
| 24 | F | 43 | NA | Nickel sulphate, fragrance mix*, black rubber mix, gold sodium thiosulphate | Presented in the label of the makeup remover used |
| 25 | F | 18 | Student | Cobalt chloride, carba mix*, black rubber mix* | Started with the use of swimming goggles |
| 26 | F | 51 | Housewife | Nickel sulphate | No cosmetic use (ectopic exposure) |
| 27 | F | 22 | Student | Colophonium | Presented in the label of the eye cosmetics used |
| 28 | M | 23 | Carpenter** | Potassium dichromate*, gold sodium thiosulphate | Presented in the label of the wood preservatives and varnishes used occupationally (aeroallergen) |
| 29 | M | 31 | Teacher | Cobalt chloride, hidrocortisone-17 butyrate* | Started with the use of 0.1% locoderm cream (hydrocortisone-17 butyrate) on hands (ectopic exposure) |
| 30 | M | 29 | Flight personnel | Cl-Me-isothiazolinone | Presented in the label of the shampoo used |
| 31 | F | 42 | Doctor | Nickel sulphate | Presented in the label of the mascara and tweezers used |
| 32 | F | 30 | Housewife | Nickel sulphate*, gold sodium thiosulphate* | Presented in the label of the metal and gold jewelry used |
| 33 | F | 22 | Student | Nickel sulphate | Dermatitis started from the area around the eyebrow piercing |
| 34 | F | 31 | Office worker | Nickel sulphate | Presented in the label of the eye cosmetics and glasses frame used |

Table 5: Continued.

| Patient no | Gender | Age | Occupation | Positive allergens | Possible clinical contactants of patients |
|---|---|---|---|---|---|
| 35 | F | 27 | NA | Potassium dichromat, balsam of Peru* | Presented in the label of the new hair cream used |
| 36 | F | 37 | Bank worker | Formaldehyde resin*, gold sodium thiosulphate, bronopol | Started with the use of hand disinfectant (ectopic exposure) |
| 37 | F | 28 | NA | Cl-Me-isothiazolinone | Presented in the label of the new makeup remover used |
| 38 | F | 28 | Office worker | Cobalt chloride*, carba mix*, gold sodium thiosulphate | Presented in the label of hair dye used.<br>She also wears gold jewelry |
| 39 | F | 32 | NA | Formaldehyde resin | Occurred following the application of gel prosthetic nails (ectopic exposure) |
| 40 | F | 38 | Housewife | Thiomersal | Started with the use of contact lenses<br>Presented in the label of the lens solution |
| 41 | M | 52 | Furniture maker** | Epoxy resin | Presented in the label of occupationally used surface coatings (aeroallergen) |
| 42 | F | 36 | Real estate agent | Caine mix, colophony, balsam of Peru* | Presented in the label of the perfume and shampoo used |
| 43 | F | 24 | Housewife | Nickel sulphate-lanolin alcohol*, gold sodium thiosulphate | Presented in the label of the makeup remover solution used<br>She also wears gold jewelry |
| 44 | F | 18 | Student | Balsam of Peru | Occurred following the use of shampoo and conditioner at a hotel |
| 45 | F | 32 | NA | Nickel sulphate*, cobalt chloride | She wears jewelry, has piercings, and uses eyelash curlers. It may also be present in the cosmetics used |
| 46 | F | 47 | Nurse | Nickel sulphate | No cosmetic use. The possibility of ectopic exposure from keys, money, and kitchen utensils was considered |
| 47 | F | 43 | NA | Colophonium*, gold sodium thiosulphate* | Presented in the label of the mascara used<br>She also wears gold jewelry |
| 48 | F | 18 | Textile worker** | Quinoline mix, disperse blue 106* | Developed after she started working in the textile sector. She has occupational exposure to fabric dyes (ectopic exposure) |
| 49 | F | 20 | NA | Quaternium 15 | Presented in the label of the facial cleansing gel used |
| 50 | F | 38 | Textile worker | Fragrance mix*, cobalt chloride | Presented in the label of the shampoo used. She also uses cologne frequently (direct + ectopic exposure) |
| 51 | F | 32 | Nurse | Colophonium*, paraben mix | Presented in the label of the nail varnish used (ectopic exposure) |
| 52 | F | 41 | NA | Fragrance mix | Presented in the label of the perfume and cosmetics used (direct + aeroallergen) |
| 53 | M | 20 | Student | Balsam of Peru, formaldehyde resin* | Presented in the label of the disinfectant used (ectopic exposure) |
| 54 | F | 41 | NA | Caine mix | History of numbing cream use on the face before fractional laser |

F: female; M: male; NA, not available, *Allergen found to be clinically relevant in patients with more than one allergen positivity, **Patients diagnosed with occupational contact dermatitis.

been reported as the most common allergens responsible for periorbital dermatitis [7–12]. Similarly, in the current study, the allergens that were most commonly identified as positive were nickel sulfate (31.0%), gold sodium thiosulfate (19.0%), fragrance mix (13.8%), balsam of Peru oil (10.3%), colophonium (10.3%), cobalt dichloride (8.6%), p-tert-Butylphenol formaldehyde resin (6.9%), thimerosal (5.2%), quaternium-15 (5.2%), carba mix (5.2%), and potassium dichromate (5.2%).

Nickel sulfate is the most frequently detected allergen, with patch test positivity in all contact dermatitis cases, not just periorbital dermatitis. In the periorbital region, the nickel content of spectacle frames, cosmetic products, and the metal parts in mascara, eye shadow, eyeliner, eye pencil, and more recently, eyelash curlers are responsible for nickel sensitivity. In the literature, the positivity rate of nickel sulfate in periorbital dermatitis has been reported in a wide range, from 8.9 to 42% [7–12]. Supporting the literature, in the current study, nickel sulfate was determined to be the most common allergen with a frequency of 31.0% in periorbital dermatitis. In previous studies conducted in Turkey reporting patch test results in patients with a prediagnosis of ACD, the rate of positivity in patch testing to nickel sulfate was reported to range from 12.2 to 29.6%. In my previous study, I determined this rate to be 16.8% [6]. However, there is no research investigating patch results only in periorbital dermatitis in a Turkish population. The frequency observed in the current study is also higher than previous reports from Turkey [6, 19–23]. This can be attributed to the inclusion of only periorbital dermatitis cases in the current sample, unlike other studies.

In this study, GST was the allergen that had the second highest frequency (19.0%). In previous studies, the frequency of gold positivity in patch testing has been reported to range from 0.8 to 14.7% [24, 25]. In a study conducted by the North American Contact Dermatitis Group (NACDG) in 2003 and 2004, gold was reported to be the most common allergen causing limited periorbital dermatitis [9]. However, after the 2003-2004 study period, NACDG excluded routinely testing for gold sensitivity due to the high frequency of irritant reactions, recommending this evaluation to be performed only when jewelry allergy was suspected or in the presence of head and neck dermatitis [6]. In a comprehensive retrospective study conducted by NACDG and published in 2021, the rate of GST positivity was reported to be 14.7% in patients with only periorbital dermatitis [10]. In my previous study, although I found a higher GST positivity (21.9%) in dermatitis cases accompanied by head-neck involvement compared to those without head-neck involvement (14.2%), I did not detect a significant difference [6]. In particular, the frequent use of gold jewelry is often responsible for GST allergies [25]. The gold sensitivity of the patients in this study was also caused by jewelry use. The high rate of positivity in patch testing observed in the current study can be attributed to the historic practice of gifting gold jewelry, particularly during weddings in Turkey [6]. It should also be noted that many cosmetic products, such as eye shadows, mascaras, and foundations, contain gold nanoparticles. Furthermore, GST is not part of the European Standard Series, commonly used for patch testing in Turkey. Thus, there is a lack of data on the prevalence of GST sensitivity in research that have reported patch test results in this country [6]. To the best of the author's knowledge, this study is the first to report the rate of GST positivity in eyelid dermatitis in a Turkish population.

According to the results of this study, the most common cosmetic allergens were the fragrance mix (13.8%), balsam of Peru oil (10.3%), colophonium (10.3%), p-tert-Butylphenol formaldehyde resin (6.9%), thiomersal (5.2%), and quaternium-15 (5.2%). As known, fragrance mix is an allergen found in many cosmetic products, such as perfumes, colognes, aftershaves, sunscreen, shampoos, makeup removers, scented detergents, and room fragrances. The T.R.U.E test includes a fragrance mix composed of eight different elements (geraniol, hydroxycitronellal, a-amyl cinnamaldehyde, eugenol, cinnamaldehyde, cinnamyl alcohol, isoeugenol, and oak moss), corresponding to fragrance mix I in the European Baseline Series (EBS). However, this test does not contain the components of fragrance mix II, which includes hexyl cinnamic aldehyde, coumarin, farnesol, hydroxyisohexyl 3, cyclohexane carboxaldehyde, and citral [25]. It has been reported that the prevalence of positive patch test results was higher for fragrance mix I than for fragrance mix II [26]. Since the current study reports the results of the T.R.U.E. test, the reported rate of fragrance mix positivity only includes fragrance mix I allergens. Some studies have reported the fragrance mix to be the most common allergen causing sensitivity in patients with periorbital dermatitis [27, 28]. In this study, the fragrance mix was the most common cosmetic allergen after metals. In studies in which the patch results of contact dermatitis were reported in Turkish populations, the rate of fragrance mix positivity varied between 2.1 and 6.4%. Similarly, in my previous work, I reported fragrance mix positivity in patients prediagnosed with contact dermatitis at a rate of 3.4% and 7.9% in the group with accompanying head-neck involvement [6]. Therefore, the rate found in the current study (13.8%) is well above the range reported in Turkey. As in the case of nickel sulfate, this finding can also be related to this study only including the results of patients with periorbital dermatitis, unlike previous studies from Turkey reporting nickel sulfate patch test results in all contact dermatitis cases without any limitation of localization. This can also suggest that ACD that develops due to the fragrance mix can be found at a higher rate in the periorbital region than in other body parts. Another important finding related to fragrance mix sensitivity in this study was that the frequency of positivity in patch testing increased among the patients aged 40 years and older. In a study investigating the prevalence of fragrance mix allergy in the Turkish population, Özkaya and Kılıç Sayar reported the patch test results of 2,566 patients and found a higher positivity rate in those aged over 40 [29]. This may be due to the decrease in the protective properties of the skin barrier and the increase in the frequency of cosmetic use with advanced age.

Other cosmetic and preservative allergens frequently found to be positive among the patients in this study were

those present in many personal care products, namely balsam of Peru oil (used as a fragrance in perfumes, shampoos, hair products, and creams), colophonium (contained in mascaras, eyeshadows, soap, shampoos, lipsticks, and nail polishes), p-tert-Butylphenol formaldehyde resin (found in skin care products, disinfectants, shampoos, and especially nail polishes to provide shine and resistance), thiomersal (used as a preservative in contact lens solutions and as an antibacterial in eye cosmetics), and quaternium-15 (found in moisturizers, shampoos, soap, and sunscreens). In a previous study, I found the positivity rates of Balsam of Peru and colophonium to be 1.7% and 1.6%, respectively. I also observed significantly higher positivity rates (7.9% and 8.8%, respectively) in the group of patients with accompanying head and neck involvement [6]. Consistently, in the current study, the positivity rate was 10.3% to both allergens among the patients with periorbital dermatitis. This result highlights the increasing frequency of cosmetic sensitivity in the periorbital region.

Sensitivity frequencies may change in populations over the years, depending on the emergence of new allergens, the reduced use of some chemicals, or the increased use of cosmetic products. In order to evaluate this change, the 11-year study period was divided into two (first and second 5.5 years) to compare the positivity frequencies of allergens. An increase was found in the frequency of positivity to nickel sulfate, GST, and colophonium in the post-2017 period, although this did not reach a significant level. In the same period, the number of patients who underwent the patch test due to eyelid dermatitis increased more than twice compared to the first 5.5 years. The remarkable increase in the use of piercings among young people in Turkey in recent years may be responsible for the increased sensitivity to nickel sulfate during this period. It is also clear that the increase in the use of jewelry and cosmetics is a reason for the higher sensitivity in the second evaluation period.

Compared to the EBS, the T.R.U.E. test does not contain the allergens 2-hydroxyethyl methacrylate, N-isopropyl-N-phenyl-para-phenylenediamine, sesquiterpene lactone mix, sodium metabisulfite, propolis, fragrance mix II, Lyral, MI, benzisothiazolinone, textile dye mix, and decyl glucoside. Other allergens that are not included in the T.R.U.E. test are oleamidopropyl dimethylamine, benzalkonium chloride, and tosylamide formaldehyde resin, which have been reported to be associated with eyelid dermatitis but have not been approved by the US Food and Drug Administration [7]. Due to the insufficient concentration or absence of some cosmetics that may be responsible for ACD in the T.R.U.E. test, patients with periorbital dermatitis need to be evaluated with additional test panels. Especially in studies reporting patch test positivity rates in recent years in Turkey, attention has been drawn to the increasing rates of isothiazolinones sensitivity [19, 30, 31]. Methychloroisothiazolinone/MI and MI are allergens commonly found as preservatives in cosmetics such as shampoos, soaps, conditioners, and gels (hair and body), which have been reported to cause significant frequency of ACD, especially between 2010 and 2015 [19]. MCI/MI is present at a concentration of 4 mcg/cm$^2$ in the T.R.U.E. test panel and at a concentration of 0.01% aq. in the EBS. In the current study, the positivity rate of MCI/MI was 4.9% between 2017 and 2022, while no positive cases were detected between 2012 and 2017. In a study undertaken by Kazan et al., the general prevalence of MI and MCI/MI positivity in Turkey was reported to be 8.4% between 2014 and 2021 [30]. Özkaya et al., on the other hand, reported this rate to be 3.3% between 1996 and 2019, emphasizing the peak positivity frequency in 2015 (16.4%) [31]. Unlike both studies, although the current study only reported the results of patients with periorbital dermatitis, the positivity frequency was determined to be lower. This can be attributed to the differences in the concentration of allergens included the T.R.U.E. test, one of the limiting aspects of the study, as well as the inability to evaluate MI due to its absence in this test panel.

This study has certain limitations. One of these limitations is that the T.R.U.E. test was conducted on all patients in the study as a standard patch test, without using any additional extended series, such as cosmetic and medication series, or testing the personal products used by the patients. In addition, there are studies indicating lower allergen positivity rates detected by the T.R.U.E. test, ranging from 10.8% to 26.7%, compared to extended standard series [6, 26]. This approach may have resulted in some allergen sensitivities going undetected. Similarly, in this study, the clinical relevance of positive patch test results could not be conclusively determined. The potential allergen exposure information obtained from patient records was assessed retrospectively. In this regard, detailed prospective studies are necessary to provide a more thorough understanding of the clinical relevance of these patch test results. In addition, the patches were applied to the patients' upper back regions. Due to the high allergen sensitivity of the periorbital region, an allergen that does not result in a reaction on the upper back may do so in the periorbital region. Lastly, this study was retrospective, and the number of patients was limited.

## 5. Conclusions

This study is the first to evaluate T.R.U.E. test results for periorbital/eyelid dermatitis in a Turkish population. Similar to other populations, ACD was found to be the most common etiological cause of eyelid dermatitis. Therefore, patch testing should be used as a regular diagnostic tool for these patients. The most common allergens detected were metals (nickel sulfate, GST, and cobalt dichloride) and cosmetics (fragrance mix, balsam of Peru oil, and colophonium). The frequency of an AD diagnosis was higher in patients with trunk involvement accompanying periorbital dermatitis compared to those with only periorbital involvement. Both the frequency of eyelid dermatitis and the frequency of positivity to nickel sulfate, GST, and colophonium increased in the second 5.5 years. There is a need for multicenter prospective studies with the evaluation of extended case series and personal products to investigate allergens that are causative agents of eyelid dermatitis in Turkey.

## Data Availability

The data used to support the findings of this study are included within the article.

## Conflicts of Interest

The author declares that there are no conflicts of interest.

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