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Contact allergy to topical ophthalmic medications: A retrospective single-centre study of three decades

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Abstract

Background: The prevalence of contact allergy to various ophthalmic medications appears to be rare; however, data on culprits, clinical relevance of sensitizations, and changes in frequency within recent decades are limited.

Objective: This study aimed to investigate the clinical relevance, risk factors, and prevalence of contact allergy to topical ophthalmic medications in patients suspected of allergic contact dermatitis to ophthalmic medication.

Methods: We retrospectively analysed patch test results and clinical data for 754 patients patch-tested with an ophthalmic medication series at our tertiary referral centre between January 1992 and December 2022.

Results: In total, 37.5% (283/754) of patch-tested patients had a contact allergy to at least one ophthalmic allergen, with 87.3% (247) being clinically relevant sensitization. Phenylephrine (31.8%, 192/604), povidone-iodine (29%, 27/93), and tobramycin (23%, 46/200) were the most important sensitizers. The incidence of contact allergies increased significantly in a linear manner ($p = 0.008$) from 20% to 44.1% within the study period. Male sex and age above 40 were risk factors for contact allergy to ophthalmic medication.

Conclusions: One third of patch tested patients had allergic contact dermatitis to ophthalmic medication, particularly phenylephrine. Male sex and age above 40 years were independent risk factors and drove the linear increase in contact allergy to ophthalmic medications within the past 31 years.

KEYWORDS

allergic contact dermatitis, contact allergy, eye drops, ophthalmic, ophthalmologic, topical eye medications

1 | INTRODUCTION

Allergic contact dermatitis caused by ophthalmic medications (OftACD) is uncommon, with a prevalence of approximately 0.7%–1% in patch test populations.^{1,2} However, among patients suspected of having OftACD, the prevalence is higher, ranging from 1/3 to 2/3 of all patch-tested individuals.^{3,4}

Clinically, OftACD typically presents as eczematous lesions in the periorbital area⁵⁻⁷; thus, OftACD may be misinterpreted as differential diagnoses commonly manifesting in this area, such as atopic and seborrheic dermatitis, irritant contact dermatitis, and ocular rosacea.^{8,9}

Therefore, patch testing is an essential diagnostic tool to diagnose or exclude contact allergy to ophthalmic medication.^{8,9} Most

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ophthalmic medications are not commercially available as patch testing solutions, which remains a clinical challenge, as these medications contain a wide range of ingredients from antibiotics to corticosteroids, antiseptics and anti-glaucoma drugs,¹⁰⁻¹² used in the treatment of various eye conditions. Thus, data on the prevalence of contact allergy to various allergens, including the proportion of clinically relevant sensitizations, are essential to improve the diagnosis and management of such patients.

This study investigated the clinical relevance, risk factors and prevalence of sensitization to topical ophthalmic medications in patch-tested patients between 1992 and 2022 in our tertiary referral centre.

2 | METHODS

2.1 | Patch testing

In this retrospective study, we assessed patients suspected of OftACD who were patch-tested with our eye medication series between January 1992 and December 2022 at the Department of Dermatology and Allergy Centre, Odense University Hospital, Denmark.

The eye medication series included ophthalmological allergens, which changed throughout the study period due to clinically derived adjustments and inaccessibility (Table 1). The allergens were commercially obtained from Trolab, SmartPractice and ChemoTechnique Diagnostics or supplied by the University Hospital pharmacy in petrolatum (pet) and aqua (aq).

The patch tests were read on day (D)3 or D4, and D7, with only reactions +, ++ or +++ categorized as positives.¹³ Negative, irritant, follicular and doubtful reactions were categorized as non-allergic responses. In the case of multiple patch tests, only the last test result was included for analysis. The present or previous relevance of a positive patch test was assessed by a trained dermatologist and evaluated according to guidelines, including exposure history and dermatitis pattern.¹³ Patch tests without registration of relevance were categorized as unknown relevance. The study population was characterized according to the MOAHLFA acronym index: M = male, O = occupational dermatitis, A = atopic dermatitis (current or previous), H = hand dermatitis, L = leg dermatitis, F = facial dermatitis, A = age > 40 years.

2.2 | Statistics

The comparisons were performed by the Chi-squared (χ^2) test of proportions, whereas the χ^2 trend test (Cochran-Mantel-Haenszel test) evaluated trends across the study period. Logistic regression analyses were conducted with contact allergy to ophthalmic medication as the dependent variable and MOAHLFA characteristic as the independent variable, adjusting for other confounding MOAHLFA variables (Table 2).

The level of statistical significance for the two-sided tests was p -value < 0.05. The results were presented as percentages and odds ratios (ORs) with 95% confidence intervals (CIs). Data analysis was performed with STATA version 18 (Stata Corporation LP®, Texas, USA).

3 | RESULTS

In total, 754 patients (504 females, 250 males) with a mean age of 59.7 years (SD: 18.7) were patch tested with the eye medication series between 1992 and 2022. Approximately 38% (283/754) of the patients had a positive patch test reaction, with 87% (247/283) being clinically relevant (Table 1).

The demographics of the patients are presented in Table 2. Male patients and age above 40 years were associated ($p < 0.001$) with positive patch test reactions. The mean ages of sensitized and non-sensitized patients were 68 and 55 years, respectively. Both risk factors remained significant ($p < 0.001$) in the adjusted logistic regression analyses. Additionally, occupational dermatitis, atopic dermatitis and hand dermatitis were negatively associated with positive patch test reactions, but these associations were diluted in adjusted analyses.

Phenylephrine (192/604) was the most common cause of positive patch test, followed by povidone-iodine (27/93) and tobramycin (46/200) (Table 1). Furthermore, sodium metabisulfite (13/174), ammoniated mercury (17/629), chloramphenicol (13/637), and timolol maleate 'as is' (10/403) also produced a relatively high proportion of positive patch tests.

The overall clinical relevance of positive patch tests to ophthalmic medications was high (87%). Notably, 97.9% (188/192) of phenylephrine sensitizations were clinically relevant. Additionally, 80% of timolol maleate (8/10 of 'as is'), 76.9% (10/13) of sodium metabisulfite and chloramphenicol sensitization, 75% (9/12) of timolol maleate in 0.5% pet., 69.6% (32/46) of tobramycin sensitization, and 63% (17/27) of povidone-iodine sensitization were also frequently found clinically relevant. Although reactions to tropicamide, tetracaine and edetic acid disodium salt were rare, almost all were clinically relevant (Table 1).

Figure 1 illustrates the prevalence of positive patch tests for ophthalmic medications between 1992 and 2022. The proportion of at least one positive patch test was 32% for females and 48.6% for males. The overall proportion was 37.5%, with a significant overall increase from 20% ($n = 45$ tested between 1992 and 2002) to 44.1% ($n = 456$ tested between 2013 and 2022), determined by a chi-square trend test ($p = 0.008$) within the study period. However, this trend was primarily driven by an increased tendency among males ($p = 0.003$) from 30.8% to 48.6% between 1992 and 2022, whereas the increase from 15.6% to 32% among females was statistically insignificant ($p = 0.064$). Seven allergens caused sensitizations throughout the study period in at least 10 patients (Table 3). Only phenylephrine, chloramphenicol and ammoniated mercury were used for patch testing throughout all three periods, but without significant change in positive proportions (χ^2 trend-test, $p > 0.05$).

TABLE 1 The prevalence of allergen sensitization and clinical relevance of the positive patch test reactions among 754 patients patch tested with the eye medication series at Odense University Hospital, Denmark, between 1992 and 2022.

Allergen	Concentration	Test period (year)	Positive patch test, % of tested patients (n)	Clinical relevance of positive patch test ^a , % (n)
All	–	1992–2022	37.5 (283/754)	87.3 (247)
<i>Active ingredients</i>				
<i>Antibiotics</i>				
Bacitracin	20% pet	1992–2022	0.3 (2/630)	50 (1)
Chloramphenicol	5% pet	1992–2022	2.0 (13/637)	76.9 (10)
Polymyxin B	3% pet	2001–2022	0.7 (4/607)	25 (1)
Tobramycine	20% pet	2017–2022	23.0 (46/200)	69.6 (32)
Sulfanilamide	5% pet	1992–2022	0.2 (1/633)	–
<i>Topical anaesthetics</i>				
Oxybuprocaine	0.4% aq	2008–2022	0.4 (2/461)	50 (1)
Tetracaine	5% pet	2015–2022	0.4 (1/276)	100 (1)
<i>Beta-blockers</i>				
Timolol (Alcon) 5 mg/mL (Oftamolol)	10% pet	2007–2010	0 (0/104)	–
Timolol maleate	0.5% pet	2007–2022	1.9 (12/634)	75 (9)
<i>Mydriatics</i>				
Tropicamide minims	1% aq	2014–2022	1.3 (4/300)	75 (3)
<i>Others</i>				
Povidone iodine	10% aq	2019–2022	27.6 (27/98)	63.0 (17)
Atropine	1% aq	2001–2022	0.7 (4/607)	50 (2)
Phenylephrine	10% aq	2001–2022	31.8 (192/604)	97.9 (188)
<i>Non-active ingredients</i>				
Sodium metabisulfite	1% pet	2018–2022	7.5 (13/174)	76.9 (10)
Benzalkonium chloride	0.1% pet, 0.1% aq (n = 5 in 2022)	1992–2022	1.2 (8/659)	50 (4)
Ammoniated mercury	1% pet	1992–2022	2.7 (17/629)	11.8 (2)
Phenyl mercuric acetate	0.01% aq	1992–2022	0.8 (5/632)	40 (2)
<i>Product tested 'as is'</i>				
Bimatoprost	0.3 mg/mL, aq	2011–2022	0.5 (2/385)	50 (1)
Dorzolamide	2% aq	2019–2022	0 (0/97)	–
Latanoprost	50% µg/mL, aq	2011–2022	0.8 (3/385)	33.3 (1)
Optimol (timolol maleate)	5 mg/mL, aq	2011–2022	2.5 (10/403)	80 (8)
Tetracaine	1% aq	2014–2022	1.7 (5/300)	75 (4)
<i>Miscellaneous</i>				
Trusopt (dorzolamide)	40% pet	2007–2019	0.2 (1/410)	0 (0)
Pilocarpine hydrochloride	1% aq	2001–2022	0.2 (1/606)	100 (1)
Resorcinol	1% pet	1992–2022	0.3 (2/634)	50 (1)
Edetic acid disodium salt	1% pet	2001–2022	0.8 (5/660)	75 (4)

^aClinical relevance (present or previous) of positive patch tests.

4 | DISCUSSION

This retrospective study covers 31 years of patch-tested patients with suspected OftACD in a tertiary referral centre, making it the most extensive study to our knowledge.

This study found that approximately one-third of all patients were sensitized to at least one ophthalmic allergen, with the majority (87%) being clinically relevant. Therefore, the data indicate that culprit allergens can, in many cases, be identified through an eye medication series, which includes a spectrum of ophthalmological contact

TABLE 2 Comparison of patient characteristics by MOAHLFA-acronym index of included patients ($n = 754$) patch tested with the eye medication series.

Index ^a	All ($n = 754$), % (n)	Positive test ($n = 283$), % (n)	Negative test ($n = 471$), % (n)	Comparison of positive and negative tests		
				χ^2 , p -value ^b	Logistic regression (OR [95% CI]) ^c	Logistic regression p -value
M	33.3 (250)	43.1 (122)	27.2 (128)	<0.001	1.97 [1.43;2.72]	<0.001
O	4.5 (34)	1.1 (3)	6.6 (31)	<0.001	0.31 [0.09;1.14]	0.078
A	9.7 (73)	4.6 (13)	12.7 (60)	<0.001	0.67 [0.34;1.33]	0.254
H	9.7 (73)	4.6 (13)	12.7 (60)	<0.001	0.64 [0.32;1.30]	0.215
L	1.5 (11)	0.7 (2)	1.9 (9)	0.182	0.93 [0.26;5.24]	0.931
F	60 (452)	64.7 (183)	57.1 (269)	0.040	1.35 [0.98;1.87]	0.065
Age > 40 years	84.1 (634)	95.8 (271)	77.1 (363)	<0.001	5.38 [2.84;10.21]	<0.001
Age mean (SD), [years]	59.7 (18.7)	68.3 (13.4)	54.5 (19.6)	<0.001 ^d		

Note: The bold values represent the level of statistical significance ($p < 0.05$).

Abbreviations: CI, confidence interval; OR, odds ratio.

^aMOAHLFA is an acronym for M, male; O, occupational dermatitis; A, atopic dermatitis (current or previous); H, hand dermatitis; L, leg dermatitis; F, facial dermatitis; A, age > 40 years.

^b p -value of χ^2 -test comparing positive and negative patch tests.

^cAdjusted for other MOAHLFA variables.

^d p -value for two sample t -test comparison of mean between positive and negative tests.

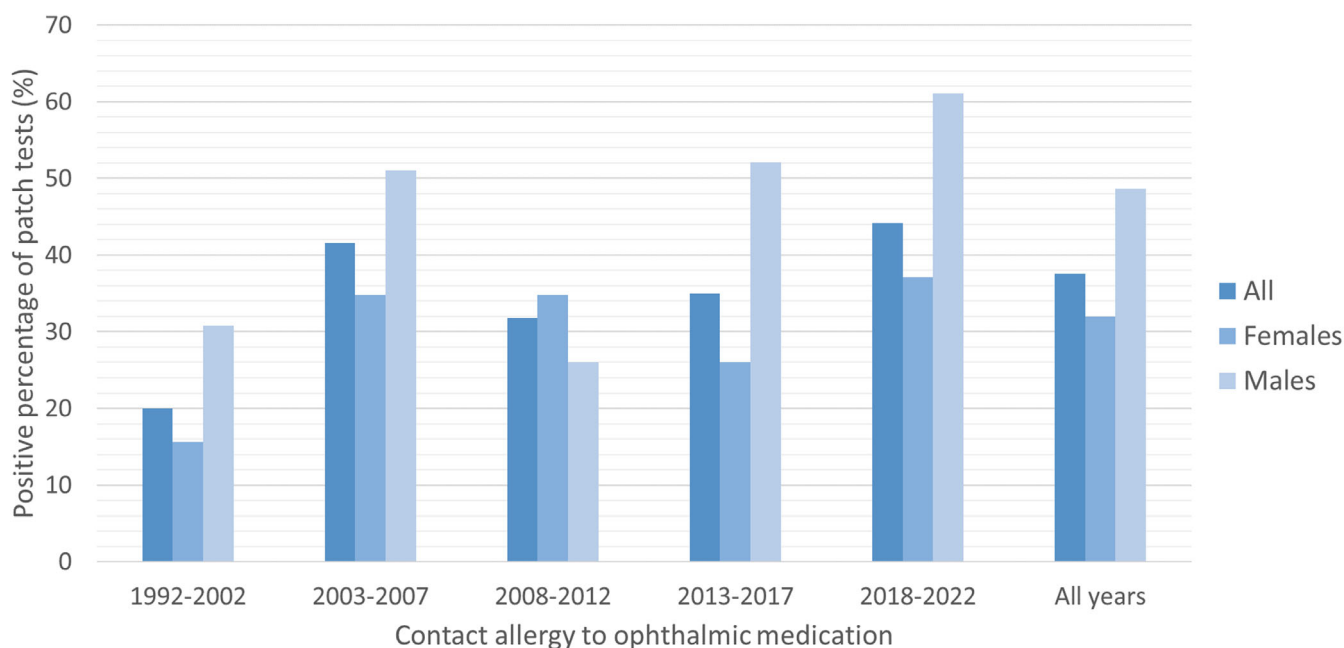


FIGURE 1 The prevalence of contact allergy to topical ophthalmic medications over time among 754 patients (504 females, 250 males) patch tested from 1992 to 2022 at Odense University Hospital, Denmark. Over the span of 30 years, from 1992 to 2022, 754 patients underwent patch testing. Among them, only 9 out of 45 patients had positive patch test results from 1992 to 2002. However, the number increased drastically to 92 out of 253 patients from 2003 to 2012. Finally, from 2013 to 2022, 182 out of 456 patients who underwent patch testing got a positive patch test result. Chi-square trend tests p -values for changes in the study period: 0.008 for all, 0.003 for males and 0.64 for females.

allergens such as antibiotics,¹⁰ corticosteroids,¹⁴ antiseptics¹¹ and anti-glaucoma treatment.¹²

The overall frequency of contact allergy to topical eye medication was higher than another recent Danish study (12.9%),⁷ lower than a Portuguese (68%) study⁴ and similar to that of other European studies (35%),^{3,4} and is probably due to various exposure patterns in these

populations. Notably, two allergens in our eye medication series produced no positive reactions, and 12 had a prevalence of less than 1%. Supplementing with the patient's own products is essential to avoid overlooking clinically relevant sensitizations.¹⁵

Phenylephrine ($n = 192$) accounted for the most common cause of sensitization, consistent with another recent Danish patch test

TABLE 3 Trends of the main sensitizing allergens (≥ 10 positive patch tests) from 1992 to 2022 at the Department of Dermatology and Allergy Centre, Odense University Hospital.

	1992–2002			2003–2012			2013–2022		
	Positive	Tested	Percent positive	Positive	Tested	Percent positive	Positive	Tested	Percent positive
All	9	45	20	92	253	36.4	182	456	39.5
Ammoniated mercury	2	35	5.7	4	240	1.7	11	354	3.1
Chloramphenicol	1	37	2.7	4	240	1.7	8	360	2.2
Phenylephrine	2	12	16.7	79	240	32.9	111	352	31.5
Povidone iodine	–	0	–	–	0	–	27	93	29
Sodium metabisulfite	–	0	–	–	0	–	13	174	7.5
Timolol maleate ^a	–	0	–	2	49	4.1	8	354	2.3
Tobramycine	–	0	–	–	0	–	46	200	23

Note: The allergen concentrations and vehicles are presented in Table 1.

^aBoth ($n = 2$) patients with positive timolol maleate 0.5% pet. had concurrent positive patch test with timolol maleate 'as is'.

study,⁷ with 98% of sensitizations being clinically relevant in our patient population. Phenylephrine is frequently applied as a topical mydriatic agent before ophthalmic examinations; thus, this finding emphasizes the importance of periorbital eczema that debuts within days after such visual inspections, as it could be a manifestation of OftACD. In such cases, it is crucial to use alternative mydriatic agents and refer patients for patch testing.

The antibacterial agents, tobramycin ($n = 46$), an aminoglycoside antibiotic, and the antiseptic agent povidone-iodine ($n = 27$), were also common sensitizers. These ophthalmic preparations are frequently used during perioperative ophthalmic procedures, emphasizing perioperative awareness of sensitization. However, povidone-iodine is an irritant causing skin irritation, leading to false positives,¹⁶ which is crucial to consider when reading the patch test. In our population, the vast majority (two-thirds) of the sensitizations were clinically relevant, indicating a requirement for special attention within days after ophthalmic surgical procedures. In the ophthalmological perioperative setting, chlorhexidine is used as an alternative antiseptic agent to povidone-iodine.¹⁷ Thus, further strength to our study would have been to include numbers on chlorhexidine delayed-type allergy; however, these data were inaccessible.

Many pharmaceutical formulations contain sodium metabisulfite, which is used as an antioxidant agent, including in topical ophthalmic medications, resulting in multiple topical exposure sources. In addition, it has found extensive use as a food preservative and disinfectant. Prevalence data on sodium metabisulfite contact allergy varies in the literature. We found that 7.5% (13/174) were sensitized to sodium metabisulfite, of which more than three-fourths (76.9%) were clinically relevant. The prevalence in our population is higher than others, including 0.9% of 4274 patch-tested in a Belgian population and being a cause of ACD among 0.1% of all tested⁴ and approximately 3.5% (76/1996) in a European Multicentre Study³ and as high as 4.5% of 2763 patch-tested in another large Belgian retrospective study.¹⁸ In 2022, patch test results on several audit allergens, including sodium metabisulfite 1.0% from an extensive network of departments (Departments of the European Surveillance System on Contact

Allergies [ESSCA]) with additional contributions from the working groups of the European Society of Contact Dermatitis and the Spanish Contact Dermatitis and Skin Allergy Research Group were published.¹⁹ Analysis was conducted on patch test reactivity and clinical relevance, showing a large number of positive reactions (3.75% of 6819 tested) to sodium metabisulfite. Because of this work, sodium metabisulfite was included in the European Baseline Series.

Ammoniated mercury is typically listed as a non-active ingredient but may be found in some ophthalmic solutions. Therefore, a thorough examination of chemical labelling is needed. In our study, approximately 2.7% (17/629) had contact allergy to ammoniated mercury, with two cases being clinically relevant (11.8%), being in concordance with 2.4% of patch-tested subjects in a multicentre study.⁸

In contrast to our study, anti-glaucoma treatments appear as frequent causes of OftACD.²⁰ However, as pure timolol maleate may cause false negative reactions,⁴ the prevalence of contact allergy to timolol maleate may exceed 1.9%, as observed in our population.

Throughout the study period (1992–2022), an increasing number of patients were patch-tested with ophthalmic medication. Additionally, the proportions of positive patch tests increased significantly in a linear manner from 20% to 44%, primarily driven by male sex and age above 40. Such observations may reflect the current demographic development throughout the health care system, with an increasing number of elderly patients in whom ophthalmological diseases such as cataracts and glaucoma are common. Phenylephrine is applied topically in the eye before various diagnostic procedures. The increasing incidence of contact allergy to phenylephrine may be attributed to the growing number of such procedures being performed. Therefore, it is crucial that healthcare professionals across various specialities, including dermatologists, general practitioners, ophthalmologists, and geriatric doctors, are aware of the clinical manifestations of OftACD in these patients.

Thus, a higher age (>40 years) was an independent risk factor for OftACD, consistent with other studies.^{1,2,7} Furthermore, despite a higher proportion of females (504 vs. 250) being patch tested, contact allergy to ophthalmic medications was found in a higher proportion of

males, thus also being a significant risk factor, in contrast to previously reported.^{1,7} We hypothesize that females are exposed to more exogenous allergens and irritants, for example, in make-up and emollients, than males, causing clinical manifestations suspicious of OftACD. Furthermore, males may be more withdrawn to undergo diagnostic ophthalmic procedures or secondary patch testing due to suspicion unless recurrent periorbital dermatitis develops, leading to a more selected population of males being tested. We did not find an association between OftACD and atopic dermatitis, a surrogate marker for patients with atopic diseases, which may be explained by these patients being exposed to various ophthalmological substances due to allergic conjunctivitis. A lack of such association may also be explained by atopic dermatitis, often clinically manifesting as head-and-neck dermatitis in adulthood, which may prompt patch testing with ophthalmic medications, potentially explaining reports of negative association reported by others.⁷ However, from a clinical point of view, OftACD manifests as eyelid dermatitis and in the periorbital region, whereas head and neck dermatitis, as the name implies, is typically distributed in the head and neck area and rarely only as eyelid dermatitis.

Eyelid dermatitis is the most common manifestation of OftACD^{1,4}; however, patients may be asymptomatic upon presenting in the clinics, leading to delayed diagnosis.⁷ Furthermore, patch testing with ophthalmic medications is challenged by frequent false negative results,²¹ possibly due to impaired penetration of allergens through thick back skin compared to the thin periorbital epidermis, which is more susceptible to sensitization.²² Moreover, numerous components, for example, antibiotics, preservatives, and pharmacologically active agents, are available for topical ocular usage but are not commercially available as patch test preparations. Obtaining pure ingredients of these topical ophthalmic medications and determining the appropriate concentration and vehicle for testing may be challenging.^{1,23} Furthermore, no standardized diagnostic protocol is available; thus, various challenges may make identifying contact allergens difficult. In case of negative patch tests but a strong suspicion of OftACD, a provocative use test (e.g., repeated open application test) can be performed.²¹ Others recommend tape-stripping prior to the patch test to increase the sensitivity, although there is a significant risk of false positive test results.²⁴ Thus, the prevalence of OftACD may be underreported.

The strengths of this study include a large study population tested throughout 31 years in a tertiary dermatological referral centre with high expertise in patch testing. In Denmark, patients can access free health care, which may prompt a low barrier for ophthalmological and dermatological diagnostic procedures, causing sensitization and detection. On the other hand, besides the MOAHLFA-indexed symptoms, we had no accessible data on the individual symptoms leading to patch testing, nor did we have data on prescribed ophthalmic medications or the use of chlorhexidine for different ophthalmic procedures and eye disorders.

However, further research concerning identifying critical ophthalmic allergens causing OftACD is required to optimize the diagnostic

procedures to ensure future treatment and maintain the patient's quality of life.¹⁵

In conclusion, this retrospective study at a tertiary referral centre reports that two-thirds of patients suspected of having OftACD had positive patch test reactions to ophthalmic agents, with the vast majority being relevant. Phenylephrine, mydriatic and antimicrobial agents were the most common sensitizers. Overall, we observed a linear increase in contact allergy to ophthalmic medication between 1992 and 2022, with male sex and age above 40 being the overall risk factors.

AUTHOR CONTRIBUTIONS

Sebastian Vigand Svendsen: Writing – original draft; writing – review and editing; formal analysis; conceptualization. **Charlotte G. Mortz:** Conceptualization; writing – review and editing. **Kristian Fredlöv Mose:** Conceptualization; writing – review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are not available due to restrictions from the Regional Committees on Health Research Ethics for Southern Denmark and the Danish Data Protection Agency.

ETHICS STATEMENT

The Allergen database (Journal no. 21/14482) and the current project (Journal no. 23/20087) were approved by the Danish Data Protection Agency.

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