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Allergic contact dermatitis by ophthalmological medications in Brazil: experience of a dermatology department

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Key words

Allergic contact dermatitis; eye drops; patch test; blepharoconjunctivitis; ophtalmic medications.

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Summary

Topical treatments in ophthalmologic therapy are significant for the development of allergic contact dermatitis (ACD) in the periorbital region. Preservatives, antibiotics, glucocorticoids, and beta-blocker eye drops are defined as drugs with the highest sensitizing potential. The unavailability of patch test batteries containing substances of ophthalmological use makes it difficult for this diagnosis. In the present report, we describe six patients who developed ACD induced by different agents presenting in eye drops, confirmed with the cutaneous patch tests. The ACD diagnosis due to ophthalmic medications can be challenging, since many different agents can cause it, and the sensitivity of these cutaneous tests is low. Thus, early diagnosis is essential to avoid the complications of ACD on the skin and ocular disorders related to chronic periorbital eczema.

Impact statement

We report six cases of allergic contact dermatitis induced by different agents presenting in eye drops, confirmed with the cutaneous patch tests.

Introduction

Ophthalmic solutions are one significant triggering factor for the occurrence of periorbital contact dermatitis or contact blepharoconjunctivitis (PCD/CBC). There are numerous components such as antibiotics, preservatives of eye preparations, and the active principles as beta-blockers used for glaucoma treatment. The thin thickness of the periorbital epidermis facilitates the permeation of allergens, making this region susceptible to sensitization, consequently resulting in allergic contact dermatitis (1).

Many cases of PCD/CBC are caused by preservatives, especially chloride benzalkonium, sodium chloride, EDTA (Ethylenediamine tetracetic acid), and thimerosal (2). However, according to recent reports in the literature, it was observed that the pharmacologically active substances are also, in large part, triggers with allergic sensitization (2).

The ACD diagnosis due to ophthalmic medications can be challenging as we observed in the literature. First, the unavailability of patch test batteries containing substances of ophthalmological use makes it difficult for this diagnosis. Second, a relatively high false-negative rate in patch testing ophthalmic agents has been reported. Grey *et al*. (3) proposed different hypotheses to explain this phenomenon such as the difference of the thickness by epidermis of the eyelid and the back or arm, sites commonly used for skin patch testing, or the low concentration of hapten in commercial products may not be sufficient to elicit response on traditional patch testing when solely testing the product itself. We describe six patients with ocular diseases conducted by the Ophthalmology and Dermatology services of our institution from January 2018 to January 2020, who presented palpebral or perior-

bital eczema or both. They were diagnosed with Allergic Contact Dermatitis (ACD) induced by the use of ophthalmic medications.

Case series

Between 2018 and 2020, six patients were referred to our service by the Ophthalmology Department because they noticed chronic periorbital pruritus and the presence of periorbital eczema. These patients underwent follow-up for eye diseases, such as glaucoma and cataract, making use of several eye drops to treat these ocular diseases.

Among the patients, four were female, two males, with an average age of 64 years (most patients older than 70 years). At first, on a dermatological examination, all presented erythema, papules, and scaly on the periorbital region and complained of local itching. Five of them had glaucoma and were under specific treatment with eye drops (**table I** and **figure 1**). None of the patients had a personal history of atopic diathesis (dermatitis, rhinitis or asthma).

Patch Test and diagnostic approach

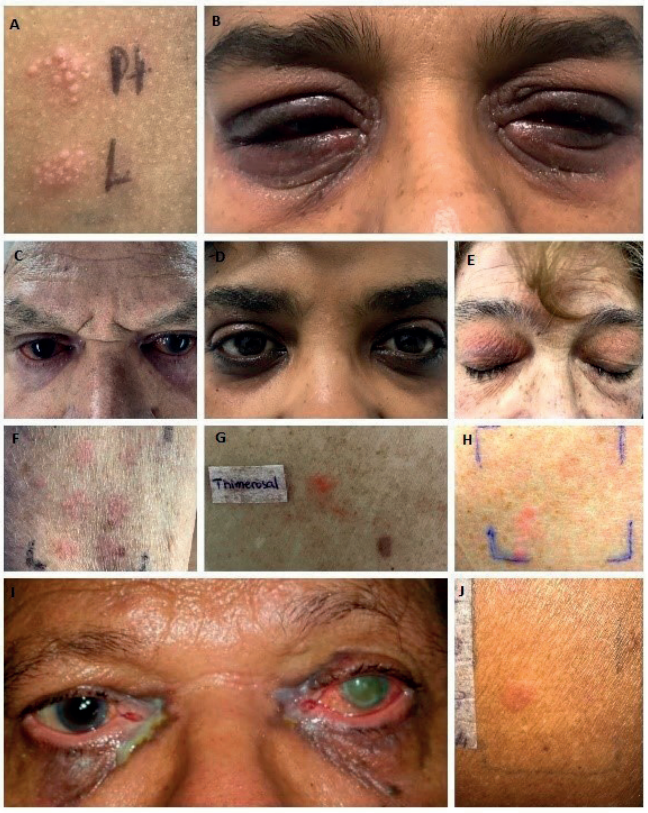
The patch test is used to detect and define possible exogenous chemical agents that can cause allergic contact dermatitis. These chemical agents can cause dermatitis by an immunologic (hypersensitivity) or non-immunologic mechanism (toxic).

The patch tests were carried out with the Standard Battery of the Brazilian Study Group of Contact Dermatitis, added with the Cosmetic Battery (4) and with the personal and continuous eye drops in use of each patient. The eye drops were tested as is, without dilution, directly in the filter paper and fixed to a Finn chamber. Two readings were performed on the tests that were applied, the first after 48 hours (D2) and the second after 96 hours (D4). The test is considered positive if erythema, edema, infiltration, and vesicles arise at the site of application of the substance and can be classified into degrees (+; + +; +++) depending on the intensity of the local reaction, as recommended by the International Contact Dermatitis Research Group (ICDRG) (4).

Table I *- Description of demographic data, ophthalmic disease, medications in use, results of late reading contact tests (96 hours reading) and clinical outcome of the 6 patients in our series.*

Patient and time of clinical complains	Eye disease (ophthalmological)	Eye drops in use	Positive substances in the late reading (D4) patch test	Clinical evolution after withdrawal of the involved substances
Patient 1. 79 yo White man 1 year	Glaucoma	Eye lubrificant Timolol Maleate 0.5% Dorzolamide 2% + Timolol 0.5% Bimatoprost Brimonidine tartrate	Timolol (+)	Full resolution of active lesions
Patient 2. 39 yo Black woman 2 months	Allergic conjunctivitis	Olopatadine hydrochloride 1.11% Alcaftadine 0.25% Sodium hyaluronate	Olopatadine hydrochloride (++) Alcaftadine (++) Ethylenediamine (++)	Absence of active injuries
Patient 3. 49 yo Black woman 2 years	Glaucoma, Keratoconus	Timolol Maleate 0.5% Travoprost 0.04 % Fluorescein Sodium	Nickel Thimerosal (++)	Improvement of eczema. Post-inflammatory dyschromia (hyperpigmentation)
Patient 4. 71 yo White woman 4 months	Glaucoma, Cataract, Bacterial conjunctivitis	Tropicamide 10mg / mL Phenylephrine 10mg / mL Hydrochloride Moxifloxacin 5.45% Prednisolone acetate 10 mg /mL Tobramycin 3 mg / mL	Prednisolone acetate (+)	Total resolution of skin change
Patient 5. 76 yo White woman 7 months	Glaucoma	Eye lubrificant Brinzolamide 10 mg / mL Timolol Maleate 0.5%	Brinzolamide (+)	Total eczema regression
Patient 6. 74 yo Black man 3 months	Glaucoma and Cataract	Atropine 0.5% Timolol maleate 0.5%	Atropine (+) Timolol (+)	Improvement of eczema

Figure 1 *- Clinical presentations and patch tests results in D4.*



(**A**) Positive Patch test to Olapatadine (++) and Alcaftadine (++). (**B**) Patient 2 described in table I. (**C**) Patient 1 described in table I. (**D**) Patient 3 described in table I. (**E**) Patient 4 described in table I. (**F**) Positive Patch test to all eye drops with Timolol (+) by Patient 1. (**G**) Positive Patch test to Thimerosal (+), (**H**) Positive Patch test to Prednisolone acetate (+). (**I**) Patient 6 described in table I. (**J**) Positive Patch test to Atropine (+).

Discussion

This study focused on characterizing the subgroup of patients referred for periorbital dermatitis with a positive patch test to ophthalmic medications during a span of 2 years. The characteristics of our patient population is similar to that of patients with periorbital dermatitis overall. A predominance of females among patients with periorbital dermatitis is well known from the literature (5-7). The female predominance has been attributed to the more common use of cosmetics and other topical products on the face. In our study, the mean age was 64 years. Landeck *et al.*, observed that patients with periorbital dermatitis related to topical ophthalmic medications were significantly older than controls and the other periorbital subgroup in a cross-sectional study with 4779 patients (7). The predominance in eldery age it was observed too in a 16,065 patients study made in Belgium (8).
Ophthalmologic solutions are an important trigger for periorbital contact dermatitis, with numerous compounds involved in the hypersensitivity reactions of contact eczemas, such as antibiotics and preservatives, including: thimerosal, benzyl alcohol, benzalkonium hydrochloride, ethylenediamine and parabens. The thin epidermis of the periorbital skin renders eyelids particularly sensitive to the hapten penetration and subsequent ACD. Glaucoma and cataract are the world's most frequents causes of acquired loss of eyesight. With the aging of the population, these pathologies are becoming more prevalent. Different kinds of eyedrops are available to control intraocular pression (IOP) in glaucoma and to retard the evolution of cataract or to prepare both for surgery intervention. It is recommended that treatment starts with only one drug, but several types of drugs are sometimes applied in combination. In such cases, the risk of contact dermatitis is more likely to increase. In recent years, the cases reports of contact dermatitis induced by different eyedrops are increasing (9, 10). The cases described include a variety of clinical presentations and severity, such erythema, papules or vesicles, swelling of the periorbital region, eyelid eczema, blepharoconjunctivits, conjunctival ecchymosis and visual blurring. Pruritus is strongly suggestive of contact allergy. Other manifestations include lichenification and postinflammatory hyperpigmentation in prolonged cases. Chronic scratching may lead to secondary infection, loss of eyelashes, or change in the tearing function.
ACD triggered by ethylenediamine, timolol, prednisolone acetate, brinzolamide, and atropine was observed in our cases, all confirmed by patch test, in a late reading (D4 or 96 hours reading). The late reading is fundamental because a sensitization reaction may occur more than 72 hours after contact. Furthermore, positive results of readings done 48 hours after application of the tests can become negative within 72-96 hours, meaning there was only local irritation due to test occlusion.
Although ophthalmic medications may be responsible for up to 20% of ACD, it is difficult to diagnose. First, the test is performed on the back which is much thicker skin than that of the eyelids and chemicals might not penetrate as easily. It is recommended to test the actual ophthalmic medication in addition to the standard ophthalmic tray available for patch testing as many chemicals in ophthalmic compositions are not a part of the commonly available kits (11). In Brazil, we do not have ophthalmic specific tray and the standard series and the lack of standardization of tests with specific batteries in Brazil since the ophthalmic substances are not part of the most available test batteries.

Conclusions

The ACD by ophthalmic drugs is becoming more frequent, caused by the increase of eye diseases diagnosis and the continuous use of topical medications. The main challenges for diagnosis are the high frequency of patch tests with false-negative in standard series. ACD by components of ophthalmic solutions must be remembered as a differential diagnosis in eyelids eczema, and periorbital regions by all practitioners, dermatologists,

allergists, and ophthalmologists considering its frequency, and the late diagnosis can bring significant eye sequelae. Further studies are needed not only to assess the appropriate concentration and vehicles for testing new drugs but also to standardize the methodology for applying unconventional patch test.

Ethics

All patients signed an informed consent form.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Amin KA, Belsito DV. The aetiology of eyelid dermatitis: a 10-year retrospective analysis. Contact Dermatitis 2006;55(5):280-5.
2. Jappe U, Uter W, Menezes de Pádua CA, Herbst RA, Schnuch A. Allergic contact dermatitis due to beta-blockers in eye drops: a retrospective analysis of multicentre surveillance data 1993-2004. Acta Derm Venereol 2006;86(6):509-14.
3. Grey KR, Warshaw EM. Allergic contact Dermatitis to ophthalmic medications: relevant allergens and alternative testing methods. Dermatitis 2016;27(6):333-47.
4. Lazzarini R, Duarte I, Ferreira AL. Testes de contato. An Bras Dermatol 2013;88(6):879-89.
5. Mughal AA, Kalavala M. Contact dermatitis to ophthalmic solutions. Clin Exp Dermatol 2012;37:593-8.
6. Kyrklund C, Alanko K, Kari O. Allergic Contact Dermatitis from Ophthalmic Medications. EC Ophthalmology 2017;8(4):115-9.
7. Landeck L, John SM, Geier J. Periorbital dermatitis in 4779 patients - patch test results during a 10-year period. Contact Dermatitis 2014;70(4):205-12.
8. Gilissen L, De Decker L, Hulshagen T, Goossens A. Allergic contact dermatitis caused by topical ophthalmic medications: Keep an eye on it! Contact Dermatitis 2019;80(5):291-7.
9. Baeck M, De Potter P, Goossens A. Allergic contact dermatitis following ocular use of corticosteroids. J Ocul Pharmacol Ther 2011;27(1):83-92.
10. Kothari M, Jain R, Khadse N, Rathod V, Mutha S. Allergic reactions to atropine eye drops for retardation of progressive myopia in children. Indian J Ophthalmol 2018;66(10):1446-50.
11. Erdinest N, Nche E, London N, Solomon A. Ocular allergic contact dermatitis from topical drugs. Curr Opin Allergy Clin Immunol 2020;20(5):528-38.