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Allergic reaction to hyaluronidase: a rare cause of orbital inflammation after cataract surgery

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Abstract *Purpose:* The aim of this study was to present a series of patients with acute orbital inflammatory symptoms secondary to peribulbar hyaluronidase allergy and to discuss the diagnostic and management modalities. *Methods:* Review of clinical records of all patients with acute orbital inflammatory symptoms after uneventful cataract surgery, seen at two ophthalmology departments. The main outcome measures included clinical signs and symptoms, imaging findings, post-operative course, skin allergy testing, and final outcome. *Results:* There were five patients (four women, one man) with a mean age of 78 ± 7.0 years. Signs and symptoms appeared 12–72 h after cataract surgery and included axial proptosis, periorbital erythema with swelling, and extraocular muscle (EOM) function restriction (5/5), periorbital pain

or itchiness (3/5), and conjunctival chemosis (4/5). Computerized tomography showed increased orbital fat haziness and enlargement of EOM. Treatment with a combination of oral antibiotics and steroids or antihistamines resulted in resolution of signs and symptoms after 3–5 days. Intradermal and/or skin prick allergy tests were positive for hyaluronidase and negative for all other perioperative medications used. *Conclusion:* Although uncommon, allergy to peribulbar hyaluronidase injected during cataract surgery should be considered in the differential diagnosis of patients who present with acute post-operative orbital signs and symptoms.

Keywords Hyaluronidase · Cataract · Orbital inflammation

Introduction

Hyaluronidase is an enzyme with a temporary and reversible depolymerizing action on hyaluronic acid present in the intercellular matrix of connective tissue. When added to local anesthetics in peribulbar or retrobulbar injections it enhances their infiltration and dispersal into the orbital tissues.

Although hyaluronidase has been commonly used worldwide for many years [3], only a small number of allergic reactions to this enzyme have been reported. In recent years, there were several reports on hyaluronidase-related orbital allergic reactions after cataract surgery [1–4, 6–8, 10].

We report five cases of hyaluronidase allergy after peribulbar injections that we treated over a period of 2.5 years. The clinical presentation, diagnosis and management are discussed.

Methods

We reviewed the medical records of all patients referred to the Royal Adelaide Hospital and Repatriation General Hospital, between January 2003 and July 2005, with acute onset of orbital inflammatory signs and symptoms after cataract surgery, and who were diagnosed with hyaluronidase allergy.

Table 1 Drugs and dilutions used for intradermal and skin prick allergy testing

Drug	Dilution used
Intradermal testing	
Cyclopentolate 1%	0.4 ml/100 ml
Phenylephrine hydrochloride 10%	0.4 ml/100 ml
Amethocaine hydrochloride 1%	0.4 ml/100 ml
Bupivacaine 0.5%	1 ml/100 ml
Ropivacaine 1%	1 ml/100 ml
Hyaluronidase 1500 IU (original batch)	750 IU/100 ml
Hyaluronidase 1500 IU (new batch)	750 IU/1000 ml
Morphine (control)	1 mg/100 ml
Normal saline (control)	0.9%
Skin prick testing	
Hyaluronidase 1500 IU (original and new batch)	1500 IU/ml
Histamine (control)	-
Thimerosal	-

IU, international units

ocular and orbital examination, computerized tomography (CT) findings, and treatment modalities. Details of intradermal and skin prick allergy tests were recorded for all patients.

Intradermal and skin prick testing were done by an experienced anesthesiologist on the patient's forearm. Drugs were freshly diluted in normal saline on the day of the test, and testing was performed using a design previously described by Fisher [6]. For prick testing the drug solution was placed on the ventral aspect of the forearm and the epidermis pricked through the solution using a 25-gauge needle, bevel uppermost at 45 deg to the skin, to a depth at which the skin could be lifted. The drugs tested and dilutions used are presented in Table 1. For intradermal testing a positive result was recorded for a persistent wheal of greater than 8 mm, and for the prick testing a positive result was recorded for a persistent wheal of greater than 4 mm [5].

Results

The data collected included cataract surgery details, postoperative clinical signs and symptoms, findings on

There were five patients (four women, one man) with a mean age of 78±7.0 years (range 70–87 years) who pre-

Table 2 Demographics and clinical presentation of patients with acute orbital inflammatory symptoms after cataract surgery

Patient	Age (years)/sex	Time since previous cataract surgery (side)	Current surgery (side)	Time to symptom onset (h)	Post-operative signs and symptoms							CT findings	
					Proptosis (mm)	EOM restriction	Erythema	Periorbital Swelling	Pain	Itchiness	Conjunctival chemosis	Fat	Enlarged EOM
1	75/F	1 year (R)	Phaco + IOL (L)	12	2	Medial	+	+	+	+	Mild	Increased haziness	MR
2	87/F	1 year (R)	Phaco + IOL (L)	24	2	All directions (mild)	+	+	+	+	Mild	Increased haziness	All recti
3	70/M	-	Phaco + IOL (L)	24	3	Lateral and upgaze	+	+	+	-	-	Increased haziness	LR + IR
4	85/F	2 months (R)	Phaco + IOL (L)	48	2	All directions (mild)	+	+	-	-	Moderate	Increased haziness	All recti
5	75/F	3 years (R)	Phaco + IOL (L)	72	4	All directions (moderate)	+	+	-	+	mild	Increased haziness	All recti

Phaco, phacoemulsification; IOL, intraocular lens; EOM, extraocular muscles; MR, medial rectus; LR, lateral rectus; IR, inferior rectus

sented with acute onset of orbital inflammatory signs after cataract surgery on the same side. These cases were diagnosed over a period of 2.5 years. During this period, 3,900 cataract operations using hyaluronidase were performed, yielding an estimated incidence of 0.13%.

All patients underwent uneventful cataract surgery using a standard phacoemulsification technique with intraocular lens implantations (Table 2). Four of the patients had been submitted to previous cataract surgery in the other eye, 2 months to 3 years earlier.

Preoperative topical drops included cyclopentolate 1%, phenylephrine hydrochloride 10%, and amethocaine hy-

drochloride 1%. Peribulbar injections contained 0.5% bupivacaine or 1% ropivacaine mixed with 100–300 IU of hyaluronidase (Hyalase; Aventis Pharma, NSW, Australia). Topical postoperative treatment included tobramycin and dexamethasone, 4 times a day. All patients experienced immediate improvement in visual acuity after the operation.

The clinical signs and symptoms are summarized in Table 2. Symptoms appeared 12–72 h after cataract surgery. Axial proptosis (ranging from 2 mm to 4 mm), periorbital erythema and swelling (Figs. 1a and 2a), and various degrees of extraocular muscle function restriction

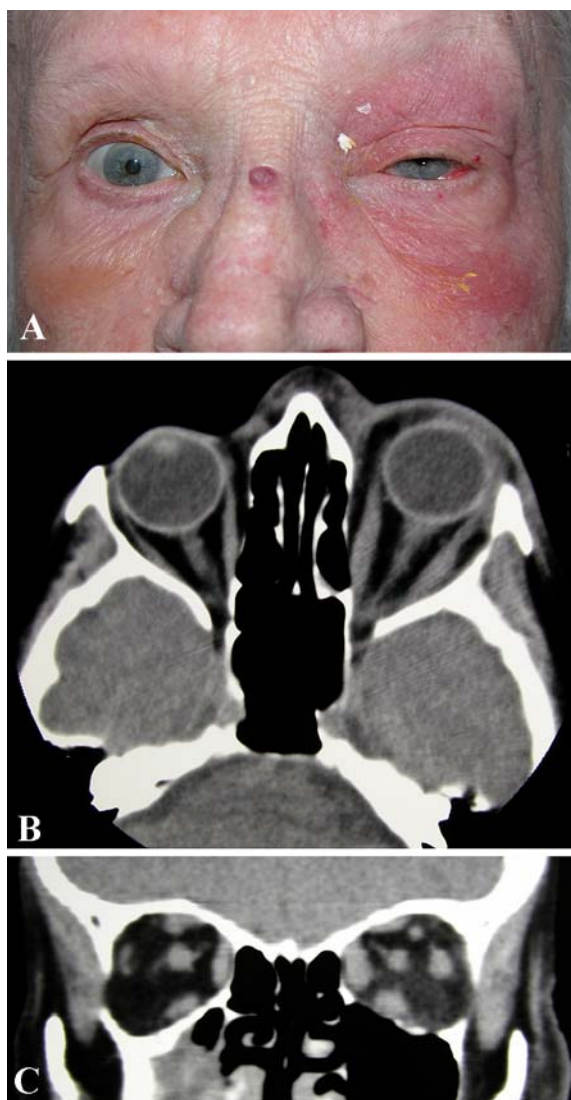


Fig. 1 **a** Clinical photograph of patient 2, who presented with left proptosis, periorbital erythema, swelling and restriction of gaze in all directions 24 h after left cataract surgery. **b** Axial computerized tomography (CT) shows left proptosis with soft tissue swelling and enlargement of the left medial and lateral rectus muscles. **c** Coronal CT shows increased haziness of orbital fat and enlargement of all four rectus muscles

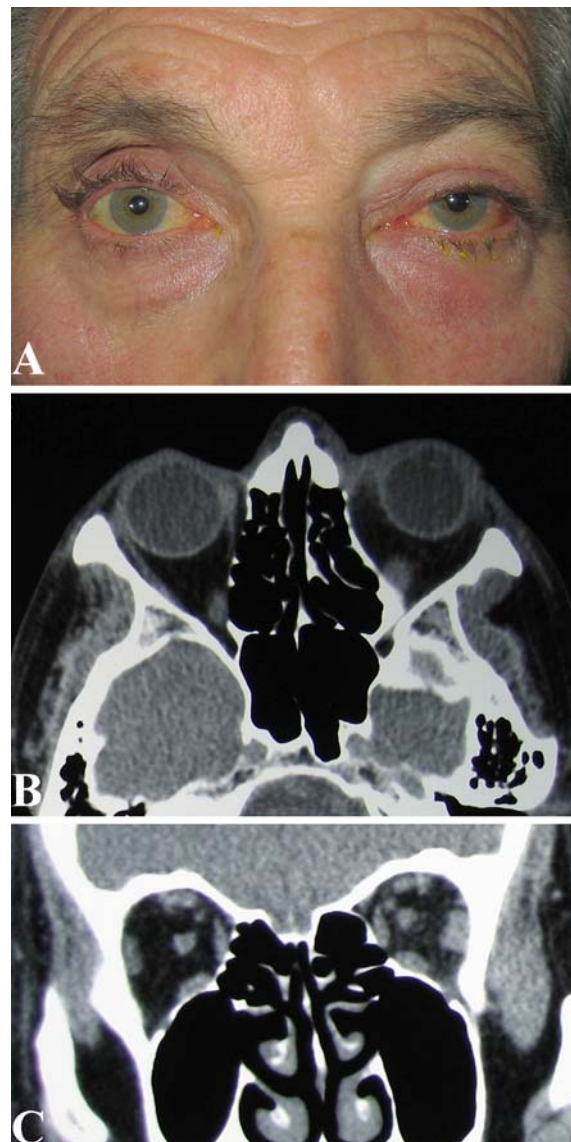


Fig. 2 **a** Clinical photograph of patient 3, who presented with left proptosis, periorbital erythema, swelling and restriction of lateral and upgaze, 24 h after left cataract surgery. **b** Axial CT shows left proptosis with soft tissue swelling. **c** Coronal CT shows increased haziness of orbital fat and enlargement of the inferior and lateral rectus muscles

appeared in all five patients. Periorbital pain or itchiness appeared in three of the patients. Conjunctival chemosis was mild in three patients and moderate in one patient. None of the patients complained of significant visual deterioration. The cornea and anterior chamber were clear in all patients, the fundus examination and intraocular pressure were normal, and there were no signs of optic nerve compromise (no relative afferent pupillary defect, normal color vision and visual field on confrontation).

All patients were not febrile and were systemically well. A complete hematological workup, including complete blood count, erythrocyte sedimentation rate, C-reactive protein, electrolytes, and liver and thyroid function tests, was normal. Serological markers (rheumatoid factor, antinuclear antigen, antineutrophil cytoplasmic antibody, angiotensin-converting enzyme) were all negative.

All patients underwent orbital CT imaging. The characteristic findings included relative proptosis and periorbital tissue swelling. In addition, in all cases there was increased haziness of the orbital fat and enlargement of some or all of the rectus muscles (Table 2; Figs. 1 and 2). There were no signs of any localized orbital pathologies or obvious sinus disease.

Most patients were treated with a combination of systemic antibiotics and steroids. Patients 1 and 2 were treated with oral cephalosporin and prednisolone (1 mg/kg), which resulted in resolution of signs and symptoms after 3 days of treatment. Patient 3 was initially treated with oral amoxicillin and clavulanic acid for 2 days, with some worsening

in symptoms. The addition of oral prednisolone (1 mg/kg) resulted in resolution of symptoms 3 days later. Patient 4 was treated with oral amoxicillin and prednisolone, with a similar resolution after 3 days. Oral steroids were gradually tapered in all four patients over a period of 10–14 days. Patient 5 was treated with intravenous cephalosporin and oral antihistamines, and the symptoms gradually resolved in 5 days.

All patients underwent intradermal and/or skin prick allergy tests for all the perioperative medications used (Table 3). Patients 1 and 2 had an immediate positive skin prick test to the original and a new batch of the hyaluronidase. The skin tests to all other medications used were negative. Patients 3 and 5 had an immediate positive intradermal test to the original and a new batch of the hyaluronidase, and negative tests to all other medications tested. Patient 4 had an initial negative result to intradermal and skin prick testing. However, after 6 h, the site of skin pricking tested positive (6 mm of wheal).

Discussion

We describe the cases of five patients with acute orbital inflammation after cataract surgery who were diagnosed with allergy to hyaluronidase, based on skin testing. Allergy to peribulbar or retrobulbar hyaluronidase is not common. The true incidence is probably slightly higher than the 0.13% that we found in our series, as some mild allergy cases are not brought to medical attention or are incorrectly diagnosed.

While reviewing the literature, we found eight reports of 14 patients who presented with acute inflammatory signs after cataract surgery (Table 4). Twelve of these cases had positive allergy skin tests to hyaluronidase. The largest, and one of the earliest series was reported by Kempeneers et al. [6] in 1992. They presented five patients; four of them proved to have a positive skin test to hyaluronidase. In a series published recently by Eberhart et al. [4], the authors describe three patients with angioedema related to the use of hyaluronidase in cataract surgery. They do not describe any obvious signs of orbital inflammation, but mention that all three patients had post-operative itching and angioedema, and that subsequent skin testing for hyaluronidase allergy was positive.

The clinical presentation in most cases is very similar. The symptoms usually appear within the first 3 days after operation, but in some previous cases they have presented acutely during the operation [7, 10]. The main symptoms are itchiness, swelling, and mild to moderate degrees of periocular pain [1, 2, 4, 6, 8]. Similar to our cases, the physical examination showed mild to moderate degrees of axial or non-axial proptosis, restriction in EOM function, periorbital erythema, edema, and chemosis. The cornea and anterior chamber are usually clear, and the fundus is normal. Although there are usually no signs of optic nerve

Table 3 Reaction to drugs used for intradermal and skin prick allergy testing

Drug	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Intradermal testing					
Cyclopentolate	-	-	-	-	-
Phenylephrine hydrochloride	-	-	-	-	-
Amethocaine hydrochloride	-	-	-	-	-
Bupivacaine	-	-	NT	NT	NT
Ropivacaine	NT	NT	-	-	-
Hyaluronidase (original batch)	NT	NT	+	-	+
Hyaluronidase (new batch)	NT	NT	+	-	+
Morphine (control)	+	+	+	+	+
Normal saline (control)	-	-	-	-	-
Skin prick testing					
Hyaluronidase (original and new batch)	+	+	NT	+	NT
				(delayed)	
Histamine (control)	+	+	NT	+	NT
Thimerosal	-	-	-	-	-

NT, not tested

Table 4 Summary of previous cases diagnosed as a post-operative allergic reaction to a peribulbar or retrobulbar hyaluronidase injection

Study	No. of patients	Inflammatory orbital signs	Positive allergy skin test to hyaluronidase	Previous ocular surgery with hyaluronidase
Taylor and Pollowitz (1984) [10]	1	Yes	Yes	NA
Kempeneers et al. (1992) [6]	5	Yes	4 patients	4 patients
Minning (1994) *	1	No	Yes	Yes
Kirby et al. (2001) [7]	1	NA	Yes	NA
Ahluwalia et al. (2003) [2]	1	Yes	Yes	NA
Agrawal et al. (2003) [1]	1	NA	Yes	No
Eberhart et al. (2004) [4]	3	NA	3 patients	1 patient
Quhill et al. (2004) [8]	1	Yes	NA	Yes
Our study	5	Yes	5 patients	4 patients

NA, data not available or incomplete data

*Minning CA (1994) Hyaluronidase allergy simulating expulsive choroidal hemorrhage. Arch Ophthalmol 112:585-586

compromise, several cases presented with visual deterioration [2, 8].

Another important clinical aspect is the lack of any systemic findings. All our patients were not febrile, were generally feeling well, and had normal blood counts and ESR. Similarly, all other previously reported cases did not show any systemic involvement.

CT is an important imaging tool in establishing the diagnosis of orbital inflammation and in excluding other orbital pathologies. The characteristic findings in all our cases were the relative proptosis, periorbital soft tissue swelling, and the increased orbital fat haziness. The degree of extraocular muscle involvement varied among cases; all rectus muscles were enlarged in three cases, whereas in the other two cases only one or two muscles were involved. The findings on orbital imaging were not clearly documented in some of the previous reports, but in those cases where CT was performed, the authors reported findings very similar to those in our patients [8].

Skin allergy testing is a very important tool in the diagnosis and management of patients with a suspected hyaluronidase allergy. Intradermal and skin prick testing are common methods used for determining the drug responsible for anesthetic type 1 (IgE-mediated) anaphylactic reactions [5]. These same methods were utilized to determine allergic reactions to other non-anesthetic agents, as in our cases and in previous reports. All our patients tested positive to hyaluronidase; two had an immediate reaction in the intradermal test and two in the skin prick test. The fifth patient had no immediate skin reaction but developed a delayed positive reaction after several hours (Table 3). To avoid any misdiagnosis of allergy based on a damaged batch, we tested the same hyaluronidase batch, as

well as a different one. In both situations, the allergy results were identical.

The exact type of hypersensitivity reaction induced by hyaluronidase is not clear. Many of the reported cases [4, 6, 8], as well as four of our patients, had a previous cataract or other ocular surgery where hyaluronidase was added to the anesthetic injection, pointing to the possibility of a IgM/IgG or T-cell-mediated allergic reaction. However, some had no previous surgical exposure to hyaluronidase, and their symptoms could represent a delayed type 1 (IgE-mediated) hypersensitivity reaction. This type of reaction was also suspected in some of the previous cases in which the inflammatory signs developed only several minutes after the anesthetic injection [1, 7] and was also reported in oncological pediatric patients who were treated with intravenous hyaluronidase injections [9].

Both intradermal and skin prick testing were successfully used to verify the drug responsible for an anaphylactic response during anesthesia and to predict the safety of alternative drugs [5]. However, these tests were not validated for topical ophthalmic medications or for drugs causing local orbital allergic reactions. The interpretation of our results should, therefore, take into account the possibility of poor sensitivity or specificity. Furthermore, it is not possible, based on these findings only, to recommend pre-operative skin allergy testing for hyaluronidase or other medications used during cataract surgery in patients with suspected allergy.

Treatment of patients presenting with acute orbital signs and symptoms during or after cataract surgery is challenging. Acute intraoperative proptosis and periorbital pain should raise the suspicion of intraorbital hemorrhage, and might require immediate intervention. Orbital cellulitis can

present as post-operative proptosis, erythema and pain and require intravenous antibiotic treatment or even surgical intervention. Being relatively rare, the diagnosis of an allergic post-operative orbital reaction should therefore be considered only after other potential sight- or life-threatening complications have been excluded, based on the clinical and radiological findings. The lack of systemic pyrexia, the general good condition of the patient, and the normal blood tests are sometimes helpful in establishing the diagnosis. We treated all of our patients with systemic antibiotics and administered combined systemic steroids in four of them, while closely monitoring the response to treatment. Systemic antibiotics were started because the possibility of infectious cellulitis could not be ruled out when the patients initially presented with the clinical signs and symptoms. From our experience, once treatment with steroids is started, symptoms start to resolve within 24 h. In

one of our patients (patient 3), who was initially treated only with systemic antibiotics, there was gradual worsening in symptoms, but once steroids were added, the symptoms quickly resolved within 3 days. In another patient (patient 5), who was treated with systemic antibiotics and antihistamines, but with no steroids, the resolution of symptoms was slower.

In conclusion, an allergic reaction to peribulbar hyaluronidase can be the cause of acute orbital inflammation after cataract surgery. The history and clinical presentation, the findings on CT, and a positive skin allergy test help establish the diagnosis. Although signs and symptoms usually improve within a few days, systemic steroids may contribute to a more rapid resolution. Hyaluronidase should not be added to local anesthetic solutions in any future ocular procedures in these patients, and the patients should be advised accordingly.

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