

Impact of allergy and atopy on the risk of pseudophakic cystoid macular edema

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Abstract

Purpose To assess the risk of pseudophakic cystoid macular edema (PCME) following cataract surgery in patients with allergies and/or atopic disorders.

Patients and methods Medical records of 3,850 consecutive eyes that underwent cataract surgery were retrospectively reviewed for prevalence of allergies and atopic status and development of PCME. Patients with any known risk factors for PCME were excluded. Macular examination was performed using spectral-domain optical coherence tomography (SD-OCT) before and at 4, 8, 12, 16, 24, and 36 weeks after surgery. If both eyes in one patient underwent cataract surgery, one eye was randomly selected. Odds ratios and confidence intervals were estimated.

Results Out of 240 patients enrolled in this series, 65 patients (27.1 %) showed positive allergic status, 19 patients (7.9 %) suffered from atopic syndromes, and 11 (4.6 %) showed both (allergies and atopic diseases). PCME occurred in eight patients (12.3 %) of the allergy cohort, whereas no patient (0 %) of the atopy cohort developed PCME. The risk of PCME was comparable in patients with allergies or atopic diseases to patients without allergies or atopy (allergy: $p = 0.635$; odds ratio (OR) 1.303, 95 % confidence interval (CI) 0.461–3.398; atopy: $p = 0.234$; OR 0.000, 95 % CI 0–1.815).

Conclusion Positive status of allergy or atopy does not seem to increase the risk of PCME. Therefore, postoperative treatment after cataract surgery does not have to be modified in allergic or atopic patients.

Keywords Allergy · Atopy · Allergens · Cataract surgery · Phacoemulsification · Macular edema

Introduction

Atopy can manifest in allergic asthma, atopic dermatitis, and allergic rhinitis. The prevalence of atopic diseases manifesting in allergic asthma, atopic dermatitis or allergic rhinitis has rapidly increased in the last decades [1]. Asthma and allergic rhinitis commonly coexist [2]. Atopic syndrome may be defined as chronic disorder of the airways in allergic rhinitis and asthma or as chronic pruritic inflammatory skin disorder in atopic dermatitis [2, 3]. These atopic diseases are characterized by hyper-responsiveness and inflammation usually described as eosinophilic, although other inflammatory subtypes are also reported [2]. Patients suffering from atopic diseases are predisposed to have allergies, such as food allergy [2, 4]. Interestingly, in patients with atopic syndrome cataract may occur earlier, and the incidence of cataract has been reported to be increased [5, 6]. Cataract is known to be the most common cause of visual impairment worldwide [7]. One important complication following cataract surgery is termed Irvine–Gass syndrome, which means the development of a pseudophakic cystoid macular edema (PCME) [8, 9].

Several studies have identified higher levels of specific cytokines in the aqueous humor as predictive factors for pseudophakic cystoid macular edema following cataract surgery in diabetic patients or patients with retinal vein occlusion, including interleukin-1 β (IL-1 β), IL-6, IL-8, IL-10, IL-12,

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interferon-induced protein-10 (IP-10), monocyte chemotactic protein-1 (MCP-1), and vascular endothelial growth factor (VEGF) [10, 11]. In line with this, systemic treatment with anti-IL-6 antibody (tocilizumab) has been shown to reduce uveitic macular edema [12]. The influence of type 2 Th cytokines such as IL-4, IL-5, and IL-13 on development of macular edema has not been explored up to date. In allergic state, an increased level of circulating IgE with upregulation of T helper (TH) 2 cytokines such as Interleukin (IL)-4, IL-5 and IL-13 can usually be observed [2, 13, 14]. It is conceivable that type 2 Th skewing could affect intraocular levels of type 1 Th cytokines such as IL-1 β , IL-6, and IL-12, thereby indirectly influencing macular thickness.

The incidence of PCME seen in optical coherence tomography (OCT) range from 4 % to 20 % [15, 16]. The pathogenesis is known to be multifactorial. Inflammation from cataract surgery is most likely to cause PCME, which can be more easily exacerbated by ocular comorbidities that promote retinovascular permeability, such as retinal vein occlusions, uveitis, and diabetic retinopathy [17, 18]. Whether growth/inflammatory factors or cytokines play an equally important role in the pathogenesis of PCME in eyes devoid of comorbidities such as diabetic retinopathy, uveitis, or vein occlusion is still unclear. Furthermore, there is no clear evidence whether chronic inflammatory diseases, such as allergic or atopic syndromes, may be associated with an increased risk of PCME, as likewise complex inflammatory disease with multifactorial etiology.

The purpose of the present study was to evaluate retrospectively whether allergic state or atopic syndromes are associated with an increased risk of PCME.

Patients and methods

Between January 1, 2010 and December 31, 2014, 3,850 eyes of 2,655 patients underwent phacoemulsification with posterior chamber intraocular lens (IOL) implantation at the Department of Ophthalmology, University of Cologne, Cologne, Germany.

Inclusion criteria for this retrospective, single-center, cohort study included cataract surgery with posterior chamber intraocular lens (IOL) implantation. Furthermore, only patients with known status of allergy and atopy in which macular examinations using spectral-domain optical coherence tomography examinations (SD-OCT) had been performed were included.

Exclusion criteria were vascular retinal diseases, manifest uveitis, non-perforating and perforating trauma, neovascular macular degeneration, chronic inflammatory conditions, diabetic retinopathy, endophthalmitis, vitreomacular traction syndrome, and previously performed pars plana vitrectomy with epiretinal membrane peeling, including surgery for macular

holes and combination of cataract extraction with ab interno glaucoma surgery (trabecular aspiration or ab interno trabeculotomy) or pars plana vitrectomy. Eventful cataract surgery, such as posterior capsular rupture or iris trauma, prolonged ultrasound time (≥ 100 s) and cumulative dissipated energy (time taken in seconds to complete a case of phacoemulsification) (≥ 20 s) during surgery, as well as postoperative pseudophacodonesis, were also considered as exclusion criteria.

Eyes meeting inclusion and exclusion criteria were enrolled consecutively in the present nonrandomized retrospective study, which was performed in conformance with the tenets of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of the Faculty of Medicine of the University of Cologne (ID 15–300).

Allergy and atopy status

Status of allergy and atopy was obtained from all patients using standardized interviews and questionnaires prior to cataract surgery. Allergy status was categorized according to the triggering allergens: pollen, drug, food, house dust mites, and other allergens. Atopy status was grouped into atopic dermatitis, allergic asthma, and allergic rhinitis [19, 20].

Surgical technique and postoperative treatment

Cataract extraction was performed in a standardized fashion by bimanual phacoemulsification followed by posterior chamber lens implantation.

Postoperative regimens included prednisolone acetate administered four times daily and tapered over 4 weeks, and a fluoroquinolone administered four times daily for 2 weeks.

Macular examinations

All eyes underwent macular examination using SD-OCT (SPECTRALIS® HRA + OCT III, Heidelberg Engineering GmbH, Heidelberg, Germany). The specific scan protocol was a custom raster scan pattern with 37 sections (512 A-scans each) in a $30^\circ \times 20^\circ$ field of view.

OCT examinations were performed before as well as 4, 8, 12, 16, 24, and 36 weeks after cataract surgery, and were analyzed retrospectively with regard to the presence or absence of PCME.

PCME was defined by the presence of newly emerged extracellular cystic spaces in the macular area in postoperative SD-OCT examinations [8, 9].

A second independent examiner re-analyzed the SD-OCT scans whether PCME was present or not. Only eyes in which both observers met the same decision with regard to the presence or absence of PCME were included in the statistical analyses.

Statistical analyses

Statistical analyses were performed using the programming language R V 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were performed for demographic data. Fisher's exact test was performed to evaluate the influence of defined risk factors (positive status of allergies and/or atopic syndromes) on the overall development of PCME; odds ratios (OR) and 95 % confidence intervals (CI) were estimated. Generalized Fisher's test was applied to determine the influence of the number of allergies or atopic diseases on PCME development. *P*-values < 0.05 were considered statistically significant.

Results

Demographics

Two hundred and forty patients (132 females and 108 males) met all inclusion and no exclusion criteria. Mean age $\pm$ SD of the overall study population was 73.0 ± 10.0 years (range, 40–94 years).

Sixty-five patients (27.1 % of overall study population; mean age 72.0 ± 10.0 years) had a positive history of any allergy (≥ 1 allergy). History of at least one atopic disease was present in 19 patients (7.9 %; mean age 68.0 ± 8.2 years), and 11 patients (4.6 %; mean age 68.0 ± 6.7 years) suffered from both allergy and atopy.

One hundred and seventy-five patients (72.9 %; mean age 74.0 ± 11.0 years) were devoid of allergy, whereas 221 patients (92.1 %; mean age 74.0 ± 10.1 years) were devoid of atopic status. One hundred and sixty-seven patients (69.6 %; mean age 74.0 ± 10.0 years) showed neither any allergy nor any atopic disorder.

Development of PCME and association of allergy and atopy with PCME

In eight patients (12.3 %) with ≥ 1 allergy, PCME was detected, whereas in 17 patients (9.7 %) without any allergies PCME occurred. None of the patients (0 %) of the atopy cohort developed PCME, and 25 patients (11.3 %) of the control cohort developed PCME.

Neither the positive history of allergy (Fisher's exact test: $p = 0.635$; odds ratio (OR) 1.303, 95 % confidence interval (CI) 0.461–3.398) nor the positive history of atopy (Fisher's exact test: $p = 0.234$; OR 0.000, 95 % CI 0–1.815) were significant predictors of development of PCME (Table 1).

Using generalized Fisher's test, no association between number of allergies or atopic diseases and PCME development could be revealed ($p = 0.64$, and $p = 0.234$; Fig. 1).

Discussion

Inflammatory disorders such as autoimmune and atopic diseases are characterized by inappropriate immune responses with regard to magnitude, duration, and target. This can result in the destruction of healthy bystander tissue, and is accompanied by systemic release of numerous cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α , which can lead to a breakdown of vascular barriers, resulting in tissue swelling such as macular edema [21]. Furthermore, susceptibility to specific inflammatory diseases is associated with a deviation of the systemic immune response into specific types such as type 1 and type 17 helper T cell (Th) responses in autoimmune diseases and type 2 Th responses in allergies and atopy [22]. This priming can have a major impact on how the immune system reacts under various conditions, for example with regard to specific microbes or surgical procedures.

Table 1 Impact of allergy and atopy on the risk of pseudophakic cystoid macular edema in 240 patients

Risk factor	Total number of patients: <i>n</i> (%)	Development of PCME: <i>n</i> (%)	Odds ratio	95 % confidence interval	<i>P</i> -value
≥ 1 allergy	65 (27.1 %)	8 (12.3 %)	1.303	0.461–3.398	0.635
Pollen allergy	26 (10.8 %)	3 (11.5 %)	1.138	0.203–4.251	0.740
House dust mite allergy	12 (5.0 %)	0 (0.0 %)	0.000	0.000–3.137	0.620
Drug allergy	27 (11.3 %)	3 (11.1 %)	1.085	0.194–4.036	1.000
Food allergy	11 (4.6 %)	1 (9.1 %)	0.855	0.019–6.498	1.000
Other allergens	16 (6.7 %)	2 (16.7 %)	1.247	0.130–5.992	0.676
≥ 1 atopic disorder	19 (7.9)	0 (0.0 %)	0.000	0.000–1.815	0.234
Atopic dermatitis	4 (1.7 %)	0 (0.0 %)	0.000	0.000–13.382	1.000
Allergic asthma	14 (5.8 %)	0 (0.0 %)	0.000	0.009–2.608	0.373
Allergic rhinitis	1 (0.4 %)	0 (0.0 %)	0.000	0.000–333.657	1.000

Prevalence of pseudophakic cystoid macular edema for different study cohorts is given. Respective odds ratios with 95 % confidence intervals and *p*-values are reported. Abbreviation: PCME pseudophakic cystoid macular edema. *P*-values < 0.05 were considered statistically significant

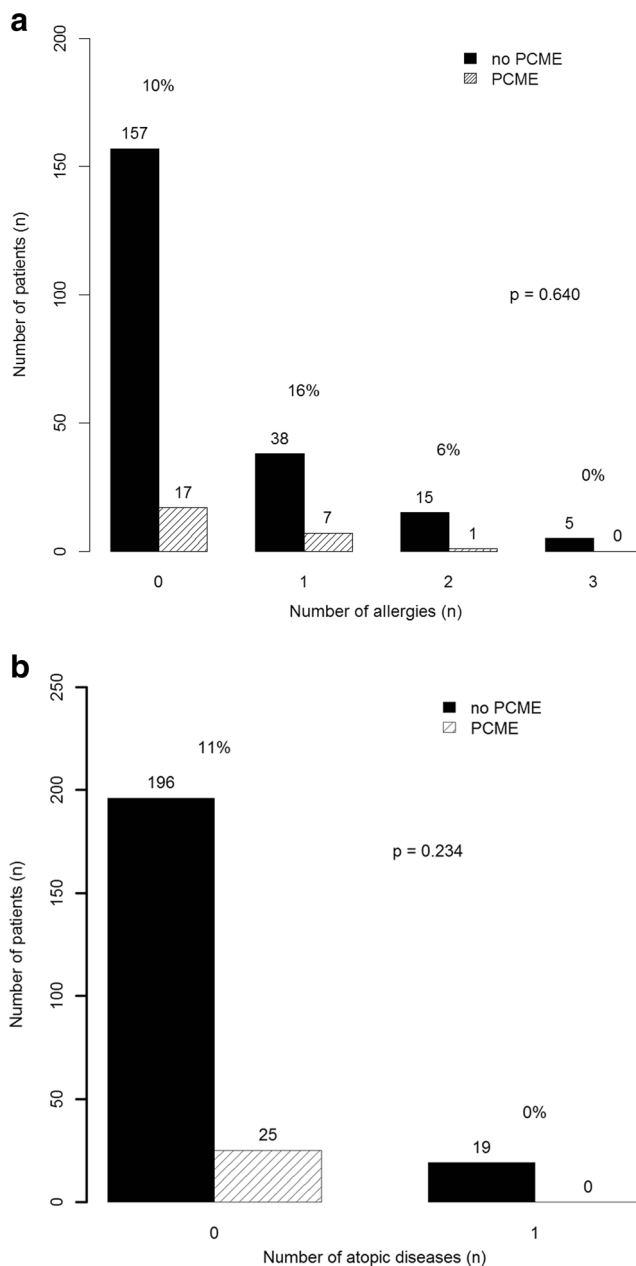


Fig. 1 Development of pseudophakic cystoid macular edema (PCME) depending on the number of co-existent allergies [none (0)–3] or atopic diseases [none (0)–1]: Absolute numbers (*n*) of patients with and without PCME development are displayed and divided into groups for the respective number of allergies (**a**) or atopic disorders (**b**). Allergy status was categorized according to the following five triggering allergens: pollen, drug, food, house dust mites, and other allergens. Atopy status was grouped into atopic dermatitis, allergic asthma, and allergic rhinitis. Respective percentages of eyes in which PCME occurred are given. *P*-values calculated by generalized Fisher's test revealed no association between number of allergies or atopic diseases and PCME development. *P*-values < 0.05 were considered statistically significant

Other environmental factors that are capable of inducing different types of immune responses include food, drugs, and pollen, among many others [23]. Interestingly, relationships between allergies or an atopic status, known to be chronic

inflammatory disorders, and ocular diseases have been frequently described [5, 6, 19, 24, 25]. Orihara et al. and Matsuda et al. reported increased prevalence of severe ocular complications, such as cataract, keratoconjunctivitis, and retinal detachment, in patients with atopic dermatitis [5, 6]. Furthermore, atopy itself constitutes a significant risk factor for immune responses even after low-risk keratoplasty [19]. Corneal allograft rejection has been supposed to be explained by a type 1 Th cellular response, but additionally a type 2 Th immune response in corneal graft rejection has been considered [26–28]. Niederkorn et al. observed in a murine model of allergic airway hyperreactivity that grafts transplanted during stable allergic periods showed lower graft failure rates than grafts placed during allergic exacerbations [29]. In contrast, Wagoner et al. could not find a relationship between type 2 Th cellular response and corneal graft survival, comparing eyes with and without a history of vernal keratoconjunctivitis that underwent corneal transplantation for keratoconus [30]. Graft survival in keratoconus eyes regarding history of atopy as a possible risk factor was examined by Thomas et al. without statistically significant difference in their results [31]. With regard to allergies, Ristau et al. detected a protective effect on the development of age-related macular degeneration (AMD) independent of the triggering allergen [24, 25].

These studies suggest an influence of the presence of allergies and atopy on the pathogenesis of several ocular diseases.

Furthermore, the role of antibodies is discussed in the literature and has been the subject of various studies. Ayaki et al. reported that auto-antibodies to lens epithelium-derived growth factor (LEDGF) result in damage to lens epithelial cells and cataract formation [32]. They speculated that cataract in atopic dermatitis may be induced by upregulation of histamine and respective intraocular higher levels of auto-antibodies to LEDGF, but no statistically significant difference was detected with regard to the prevalence of antibodies to LEDGF between atopic dermatitis patients with and without cataract [32]. Again, LEDGF was the subject of interest of Matsui et al., who were able to show that LEDGF enhanced the survival of retina pigment epithelial (RPE) cells [33] and may therefore be considered to act protectively against stress. This is the first study to evaluate a possible relationship between atopic syndromes or allergies and a clinically extremely important macular pathology, cystoid macular edema.

Cystoid macular edema (CME) is a frequent disorder that can be associated with several ocular conditions that all appear to have at least an inflammatory component, such as uveitis, diabetic retinopathy, age-related macular degeneration, macular pucker, and previously performed surgery such as cataract surgery [34–38]. However, the incidence of postsurgical CME has declined with the advent of modern surgical techniques [37]. The rate of clinical relevant PCME varies between 0 % and 6 % in uncomplicated cases [35, 37, 39]. Seen on optical coherence tomography (OCT), PCME incidence is higher (4–

20 %) [15, 16]. PCME may lead to visual decline following cataract surgery [34]. As the pathogenesis of PCME is not completely understood, it seems to be important to clarify whether a positive status of allergy or atopy may be associated with it, as previously described in AMD [24, 25], retinal detachment, or cataract [5, 6]. As mentioned before, higher levels of autoantibodies to LEDGF have been detected in various chronic inflammatory disorders and atopic diseases, or asthma, but as well as in patients with age-related cataracts [40, 41]. Whether this may be a possible reason for similar incidences of PCME in different groups of our study cohort remains unclear.

PCME was described more than 50 years ago, and there are multiple options for clinical management ranging from corticosteroid eye drops, through intravitreal anti-vascular endothelial growth factor (VEGF) application or intravitreal corticosteroid implants, to pars plana vitrectomy in refractory cases with significant vitreous involvement [8, 42–45]. Especially in diseases which are multifactorial in their pathogenesis, evaluation of risk factors is necessary in order to ensure on the one hand a risk-adapted treatment, and on the other hand to prevent side-effects of overtreatment whenever possible. In particular, patients with known risk factors for PCME development should be informed in detail about their increased risk for PCME before surgery. Furthermore, a close postoperative follow-up should be performed, in order to detect macular edema at an early stage. Both intensified topical corticosteroid application or nonsteroidal anti-inflammatory drugs are considered to prevent PCME, and therefore seem to be appropriate in high-risk patients [8, 42, 46].

This study revealed similar rates of PCME development in allergic and atopic patients compared to patients devoid of allergy and/or atopy. Furthermore, with regard to the triggering allergen no association to PCME development could be detected. Although there are limitations of our study due to a lack of laboratory testing for allergies and atopy such as IgE serum measurements and prick tests of the skin, we do not consider this to be a major problem, since our questionnaires revealed no clinically apparent manifestations of allergies and atopy that would justify extensive laboratory work-up in hundreds of these patients. Therefore, and in this clinical context, it appears appropriate to classify patients who do not have any atopic or allergy-related problems as having no allergy or atopy. Our results indicate that patients suffering from any type of allergy or atopy do not have to worry about increased risk of visual decline due to PCME. Follow-up examinations and postoperative therapy regimens do not have to be stepped up because of positive status of allergy or atopy.

Whether response to the treatment in the case of PCME or the course of PCME differs in allergic or atopic patients in comparison to healthy patients remains to be studied. Furthermore, it is unclear whether even in severe forms of

ocular allergy or atopy the rate of PCME is not increased, since we did not differentiate between light and severe forms of ocular involvement in atopy and allergy.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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References

1. Jurakic TR, Marinovic B (2014) What is new and hot in genetics of human atopic dermatitis: shifting paradigms in the landscape of allergic skin diseases. *Acta Dermatovenereol Croat* 22:313–315
2. Perry MM, Adcock IM, Chung KF (2015) Role of microRNAs in allergic asthma: present and future. *Curr Opin Allergy Clin Immunol* 15:156–162
3. Gupta D (2015) Atopic dermatitis: a common pediatric condition and its evolution in adulthood. *Med Clin North Am* 99:1269–85
4. Sabouchi S, Bollyky J, Nadeau K (2015) Review of environmental impact on the epigenetic regulation of atopic diseases. *Curr Allergy Asthma Rep* 15:33
5. Orihara T, Hirota K, Yokota R, Kunita D, Itoh Y, Rii T, Koto T, Hiraoka T, Inoue M, Hirakata A (2015) Comparison of retinal detachment associated with atopic dermatitis with that of a blunt trauma. *Nippon Ganka Gakkai Zasshi* 119:457–463
6. Matsuda A, Ebihara N, Kumagai N, Fukuda K, Ebe K, Hirano K, Sotozono C, Tei M, Hasegawa K, Shimizu M, Tamari M, Namba K, Ohno S, Mizuki N, Ikezawa Z, Shirakawa T, Hamuro J, Kinoshita S (2007) Genetic polymorphisms in the promoter of the interferon gamma receptor 1 gene are associated with atopic cataracts. *Invest Ophthalmol Vis Sci* 48:583–589
7. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP (2004) Global data on visual impairment in the year 2002. *Bull World Health Organ* 82:844–851
8. Guo S, Patel S, Baumrind B, Johnson K, Levinsohn D, Marcus E, Tannen B, Roy M, Bhagat N, Zarbin M (2015) Management of pseudophakic cystoid macular edema. *Surv Ophthalmol* 60:123–137

9. Kim SJ, Bressler NM (2009) Optical coherence tomography and cataract surgery. *Curr Opin Ophthalmol* 20:46–51
10. Dong N, Xu B, Wang B, Chu L, Tang X (2015) Aqueous cytokines as predictors of macular edema in patients with diabetes following uncomplicated phacoemulsification cataract surgery. *Biomed Res Int* 2015:126984
11. Noma H, Mimura T, Yasuda K, Shimura M (2015) Role of soluble vascular endothelial growth factor receptor signaling and other factors or cytokines in central retinal vein occlusion with macular edema. *Invest Ophthalmol Vis Sci* 56:1122–1128
12. Deuter CM, Zierhut M, Igney-Oertel A, Xenitidis T, Feidt A, Sobolewska B, Stuebiger N, Doycheva D (2016) Tocilizumab in uveitic macular edema refractory to previous immunomodulatory treatment. *Ocul Immunol Inflamm*. doi:10.3109/09273948.2015.1099680
13. Narozna B, Hoffmann A, Sobkowiak P, Schoneich N, Breborowicz A, Szczepankiewicz A (2016) Polymorphisms in the interleukin 4, interleukin 4 receptor and interleukin 13 genes and allergic phenotype: a case control study. *Adv Med Sci* 61:40–45
14. Rogala B, Bozek A, Gluck J, Jarzab J (2015) Prevalence of IgE-mediated allergy and evaluation of Th1/Th2 cytokine profiles in patients with severe bronchial asthma. *Postepy Dermatol Alergol* 32:274–280
15. Gulikilik G, Kocabora S, Taskapili M, Engin G (2006) Cystoid macular edema after phacoemulsification: risk factors and effect on visual acuity. *Can J Ophthalmol* 41:699–703
16. Perente I, Utine CA, Ozturker C, Cakir M, Kaya V, Eren H, Kapran Z, Yilmaz OF (2007) Evaluation of macular changes after uncomplicated phacoemulsification surgery by optical coherence tomography. *Curr Eye Res* 32:241–247
17. Lobo C (2012) Pseudophakic cystoid macular edema. *Ophthalmologica* 227:61–67
18. Shields MK, Adler PA, Fuzzard DR, Chalasani R, Teong JM (2015) A case of acute bilateral irvine-gass syndrome following uncomplicated phacoemulsification, demonstrated with optical coherence tomography. *Case Rep Ophthalmol* 6:143–148
19. Nguyen NX, Martus P, Seitz B, Cursiefen C (2009) Atopic dermatitis as a risk factor for graft rejection following normal-risk keratoplasty. *Graefes Arch Clin Exp Ophthalmol* 247:573–574
20. Uter W, Schwanitz HJ, Pfahlberg A, Gefeller O (2001) Atopic signs and symptoms: assessing the ‘atopy score’ concept. *Dermatology* 202:4–8
21. de Smet MD, Taylor SR, Bodaghi B, Miserocchi E, Murray PI, Pleyer U, Zierhut M, Barisani-Asenbauer T, LeHoang P, Lightman S (2011) Understanding uveitis: the impact of research on visual outcomes. *Prog Retin Eye Res* 30:452–470
22. Amadi-Obi A, Yu CR, Liu X, Mahdi RM, Clarke GL, Nussenblatt RB, Gery I, Lee YS, Egwuagu CE (2007) TH17 cells contribute to uveitis and scleritis and are expanded by IL-2 and inhibited by IL-27/STAT1. *Nat Med* 13:711–718
23. Wildner G, Diedrichs-Mohring M (2003) Autoimmune uveitis induced by molecular mimicry of peptides from rotavirus, bovine casein and retinal S-antigen. *Eur J Immunol* 33:2577–2587
24. Ristau T, Ersoy L, Hahn M, den Hollander AI, Kirchhof B, Liakopoulos S, Fauser S (2014) Nongenetic risk factors for neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 55:5228–5232
25. Ristau T, Ersoy L, Lechanteur Y, den Hollander AI, Daha MR, Hahn M, Hoyng CB, Fauser S (2014) Allergy is a protective factor against age-related macular degeneration. *Invest Ophthalmol Vis Sci* 55:210–214
26. Beauregard C, Stevens C, Mayhew E, Niederkorn JY (2005) Cutting edge: atopy promotes Th2 responses to alloantigens and increases the incidence and tempo of corneal allograft rejection. *J Immunol* 174:6577–6581
27. Hargrave SL, Hay C, Mellon J, Mayhew E, Niederkorn JY (2004) Fate of MHC-matched corneal allografts in Th1-deficient hosts. *Invest Ophthalmol Vis Sci* 45:1188–1193
28. Yildiz EH, Erdumus M, Hammersmith KM, Rapuano CJ, Laibson PR, Cohen EJ (2009) Comparative study of graft rejection in keratoconus patients with and without self-reported atopy. *Cornea* 28:846–850
29. Niederkorn JY, Chen PW, Mellon J, Stevens C, Mayhew E (2009) Allergic airway hyperreactivity increases the risk for corneal allograft rejection. *Am J Transplant* 9:1017–1026
30. Wagoner MD, Ba-Abbad R (2009) Penetrating keratoplasty for keratoconus with or without vernal keratoconjunctivitis. *Cornea* 28:14–18
31. Thomas JK, Guel DA, Thomas TS, Cavanagh HD (2011) The role of atopy in corneal graft survival in keratoconus. *Cornea* 30:1088–1097
32. Ayaki M, Ohoguro N, Azuma N, Majima Y, Yata K, Ibaraki N, Singh DP, Ko V, Shinohara T (2002) Detection of cytotoxic anti-LEDGF autoantibodies in atopic dermatitis. *Autoimmunity* 35:319–327
33. Matsui H, Lin LR, Singh DP, Shinohara T, Reddy VN (2001) Lens epithelium-derived growth factor: increased survival and decreased DNA breakage of human RPE cells induced by oxidative stress. *Invest Ophthalmol Vis Sci* 42:2935–2941
34. Bringmann A, Reichenbach A, Wiedemann P (2004) Pathomechanisms of cystoid macular edema. *Ophthalmic Res* 36:241–249
35. Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL (2007) Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. *J Cataract Refract Surg* 33:1550–1558
36. Irvine AR (1976) Cystoid maculopathy. *Surv Ophthalmol* 21:1–17
37. Vukicevic M, Gin T, Al Qureshi S (2012) Prevalence of optical coherence tomography-diagnosed postoperative cystoid macular oedema in patients following uncomplicated phaco-emulsification cataract surgery. *Clin Experiment Ophthalmol* 40:282–287
38. Zur D, Loewenstein A (2012) Combination therapy for diabetic macular edema. *J Ophthalmol* 2012:484612
39. Hunter AA, Modjtahedi SP, Long K, Zawadzki R, Chin EK, Caspar JJ, Morse LS, Telander DG (2014) Improving visual outcomes by preserving outer retina morphology in eyes with resolved pseudophakic cystoid macular edema. *J Cataract Refract Surg* 40:626–631
40. Chin MS, Caruso RC, Detrick B, Hooks JJ (2006) Autoantibodies to p75/LEDGF, a cell survival factor, found in patients with atypical retinal degeneration. *J Autoimmun* 27:17–27
41. Shinohara T, Singh DP, Chylack LT Jr (2000) Review: age-related cataract: immunity and lens epithelium-derived growth factor (LEDGF). *J Ocul Pharmacol Ther* 16:181–191
42. Almeida DR, Johnson D, Hollands H, Smallman D, Baxter S, Eng KT, Kratky V, ten Hove MW, Sharma S, El Defrawy S (2008) Effect of prophylactic nonsteroidal antiinflammatory drugs on cystoid macular edema assessed using optical coherence tomography quantification of total macular volume after cataract surgery. *J Cataract Refract Surg* 34:64–69
43. Arevalo JF, Maia M, Garcia-Amaris RA, Roca JA, Sanchez JG, Berrocal MH, Wu L (2009) Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: the Pan-American Collaborative Retina Study Group results. *Ophthalmology* 116:1481–7
44. Bellocq D, Korobelnik JF, Burillon C, Voirin N, Dot C, Souied E, Conrath J, Milazzo S, Massin P, Baillif S, Kodjikian L (2015)

- Effectiveness and safety of dexamethasone implants for post-surgical macular oedema including Irvine–Gass syndrome: the EPISODIC study. *Br J Ophthalmol* 99:979–83
45. Mitropoulos PG, Chatziralli IP, Peponis VG, Drakos E, Parikakis EA (2014) Intravitreal ranibizumab for the treatment of Irvine–Gass syndrome. *Ocul Immunol Inflamm* 23:225–31
46. Hoerster R, Stanzel TP, Bachmann BO, Siebelmann S, Felsch M, Cursiefen C (2016) Intensified topical steroids as prophylaxis for macular edema after posterior lamellar keratoplasty combined with cataract surgery. *Am J Ophthalmol* 163:174–179