

Ophthalmic manifestations of atopic dermatitis

Marta Pietruszyńska^{1,2}, Anna Zawadzka-Krajewska¹, Patrycja Duda², Monika Rogowska², Iwona Grabska-Liberek², Marek Kulus¹

¹Department of Pneumology and Allergology for Children, Medical University of Warsaw, Warsaw, Poland

²Department of Ophthalmology, Prof. W. Orłowski Independent Public Clinical Hospital, Postgraduate Centre of Medical Education, Warsaw, Poland

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Abstract

Atopic dermatitis is a chronic condition of complex etiology, whose clinical course involves remission and recurrence. It is not an isolated disease entity affecting only the skin, but one that co-occurs with disorders of other organs. Numerous literature reports have long confirmed the relationship between the disorder and a growing number of ophthalmic manifestations such as keratoconus and retinal detachment. Further studies are required to establish the cause of correlations and to allow for implementation of appropriate prophylaxis and treatment. The aim of the present paper is to review published literature regarding the correlation between atopic dermatitis and ophthalmic manifestations in adults and children.

Key words: atopic dermatitis, eye rubbing, ocular disease, keratoconus.

Introduction

Atopic dermatitis (AD) is a widespread, chronic and progressive skin disorder characterised by erythema with oedema, vesicles, and oozing lesions in the acute stage and skin thickening (lichenification) in the chronic stage [1–3]. It affects 15–20% of children and 1–3% of adults in developed countries [4]. Important causes of atopic dermatitis include genetic (e.g. loss-of-function variants in the filaggrin gene (FLG)) and environmental factors (climate, diet, breastfeeding) [4]. The extent and severity of eczema is measured using the SCORAD (Severity Scoring of Atopic Dermatitis) index [5]. Common concomitant diseases are skin conditions (skin infections, irritant contact dermatitis), gastrointestinal diseases (eosinophilic gastroenteritis), renal diseases (idiopathic nephritic disorder), autoimmune diseases (thyroid autoimmunity in children), and psychological and psychiatric disorders (sleep disturbance, abnormal interpersonal relations) [6]. The aim of this article is to demonstrate ocular complications of atopic dermatitis, namely blepharitis, conjunctivitis, tear film disturbances, keratoconus, uveitis, cataract, and retinal detachment [7–18]. The frequency of these disorders ranges from 25% to 50% [19]. Depending on disease severity, chronic treatment consists of hydration, using occlusive topical moisturisers, and application of topical steroids and topical calcineurin inhibitors [20].

Keratoconus

Keratoconus (KC) is a non-inflammatory, progressive corneal thinning disorder characterised by protrusion, irregular astigmatism and, in the final stage, scarring, which results in distorted and impaired vision [21, 22]. It usually presents as bilateral ectasia and has an incidence rate of approximately 1 per 2,000 in the general population [23]. However, for patients with AD, the incidence rate ranges from 0.5% to 39% [18, 24].

The connection between keratoconus and atopy was described by Hilgartner as early as 1937 [25]. In 1977, an article in the *British Journal of Ophthalmology* revealed that 35% of patients with keratoconus had atopic tendencies (hay fever being the most common, but also including asthma and eczema), while in the healthy control group, only 12% ($p < 0.001$) of patients exhibited such tendencies. Serum IgE levels were higher in the group with ectasia ($p < 0.001$), particularly in subjects with atopy [26]. This finding is particularly important because a significantly elevated level of this immunoglobulin can trigger graft rejection [18]. The authors of more recent studies state that despite the association between atopy and ocular manifestation in their patients, KC was not observed in patients with a low SCORAD index (Severity Scoring of Atopic Dermatitis) score [19, 27, 28]. Therefore, it could be hypothesised that KC occurs in more advanced stages of atopy.

Address for correspondence: Marta Pietruszyńska MD, Department of Ophthalmology, Prof. W. Orłowski Independent Public Clinical Hospital, Postgraduate Centre of Medical Education, 231 Czerniakowska St, 00-416 Warsaw, Poland, phone: +48 22 584 11 85, fax: +48 22 629 71 09, e-mail: martapietruszyńska25@gmail.com

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Shajari *et al.* found that out of 434 KC patients examined (670 eyes), 75 had at least 1 atopic feature and 14 at least two (asthma or AD or allergic rhinitis). The results showed that keratoconus was more frequently observed in individuals with atopy and in those who were younger. It can therefore be concluded that atopy is an early indicator of KC and that patients with a history of atopy require regular ophthalmological examinations. It was also observed that the corneal optical density of the anterior 120 μm of the cornea was higher in the group with atopy (21.92 ± 4.65 vs. 20.74 ± 4.68 , $p = 0.016$) [29].

A number of studies have demonstrated a link between eye rubbing and keratoconus [18, 30–32].

One of the symptoms of AD is itching, which stimulates eye rubbing. In unilateral cases of keratoconus, 13 out of 17 patients developed KC on the side of the dominant hand ($p < 0.05$). However, patients with unilateral ectasia lasting more than 3 years were, in fact, non-atopic or possibly non-atopic patients, which suggests that this behaviour could be a habit, while atopic patients rubbed both eyes due to itching [18]. Furthermore, a multivariate analysis performed by Bawazeer *et al.* demonstrated that eye rubbing is indeed a significant reason for the development of keratoconus. The analysis in question examined the following risk factors of keratoconus: eye rubbing, atopy and a family history of KC. The authors found eye rubbing to be the most important factor in the development of the condition ($p = 0.001$, OR = 6.31), while atopy and a family history were found to be insignificant ($p > 0.05$). On the other hand, a univariate analysis by Bawazeer *et al.* revealed that both atopy and eye rubbing were important factors of KC development [30]. Additionally, it is worth mentioning that eye rubbing is a factor in KC development not only in atopy but also in Tourette's syndrome. In an article written by Mashor *et al.*, it is reported that three patients with Tourette's syndrome exhibited KC because of asymmetric or unilateral eye rubbing [32]. The reason why eye rubbing can cause KC is unknown, but potential mechanisms have been proposed to be high temperature of the cornea, release of inflammatory mediators in the tear film and increased enzyme activity, higher intraocular and hydrostatic tissue pressure, changes in keratocytes, a decrease in corneal shear strength, and a loss of ground substance viscosity or its temporary displacement from the corneal apex [33]. In their search for answers regarding causes of KC, Sugar *et al.* posed a question: which was present first – inflammatory factors, eye rubbing or KC? [31]

A number of genes are involved in the pathogenesis of AD. In general, they can be divided into two groups: genes encoding structural epidermal proteins and genes encoding factors of the immune system [34]. The filaggrin gene (FLG) encodes structural proteins that bind keratinocytes in the stratum corneum and stratum granulosum [34]. The mutation of this gene results in skin barrier impairment and transepidermal water loss, which leads

to AD [34, 35]. An important study has been published by Droitcourt *et al.* regarding FLG mutation and KC within a population of individuals with AD. In this study, despite the fact that there were 38 patients with AD within a group of 89 patients with KC ($38/89 = 42.70\%$), only 5 of them were carriers of at least one FLG mutant allele. Moreover, the Western blot test showed no significant difference in filaggrin expression between corneas with and without ectasia. Nevertheless, those 5 individuals (mean age 21 years vs. 28.74, $p = 0.02$) suffered from a more severe type of KC and required more aggressive treatment in the form of intrastromal ring implantation (2 patients) or a corneal graft (2 patients) [36].

Therefore, additional studies concerning other FLG mutations or other genes are recommended [36].

Some allergic conditions (vernal keratoconjunctivitis, asthma, atopic dermatitis) are strongly associated with acute corneal hydrops in keratoconus, and patients with them should be examined regularly [37].

Atopic keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is a chronic inflammatory allergic disease with clinical characteristics that include conjunctivitis, corneal ulceration, superficial punctate keratitis, and corneal neovascularisation. Due to these characteristics, AKC is a condition that may potentially lead to blindness [38]. In patients with AKC, central corneal thickness is low in comparison to the control group ($523.45 \pm 18.3 \mu\text{m}$), which is important for ophthalmologists performing corneal refractive surgery, when evaluating glaucoma or keratoconus [39]. In an article by Onguchi *et al.*, the impact of AKC onset on the ocular surface was studied [40]. The authors demonstrated that the earlier the onset and the longer the duration of AKC, the more serious the ocular surface epithelial damage it causes. The AKC patients whose condition commenced in childhood had worse outcomes, which were measured by tear film instability, epithelial damage, goblet cell loss and conjunctival squamous metaplasia. The published study reinforces the significant role of early and regular ophthalmological examinations in AD patients.

Infection

The incidence of bacterial colonization in conjunctival sacs and eyelid margins in AD patients is higher in comparison to non-AD individuals (86% vs. 25%). *Staphylococcus aureus* in particular was detected in 67% of patients with AD. A study by Nakata *et al.* did not reveal correlations between the grade or duration of atopy, the type of ocular disorders, steroid use and bacterial detection rate [41]. The study results have implications for patient management. Following scleral buckling procedures, MRSA infection was detected in 18.8% of cases in the AD group in comparison to 0.4% in non-atopic patients

($p < 0.001$) [42]. Fasciani *et al.* report a case of a 22-year-old Italian patient with AD who underwent corneal cross-linking for keratoconus in the right eye. A few days after the procedure, he presented with a corneal abscess and vitreous inflammation. He was found to be positive for MRSA [43]. Both studies prove the significance of proper preoperative evaluation of patients at risk of infection, as well as postoperative management, so that infection and other serious complications may be averted.

Retinal detachment (RD)

Ocular complications of AD also include serious ophthalmological conditions such as retinal detachment. Eye rubbing may constitute a pathogenic factor – lesions at the retinal periphery are similar to those caused by trauma [44–48]. However, serum IgE levels do not have an impact on RD [47].

A review of case studies from Japan revealed one study comparing patients with atopic dermatitis from 1992 to 2001 and 2002 to 2011. This study showed that in the group of patients with atopic dermatitis treated between 1992 and 2001, there were more cases of bilateral detachment and the patients were significantly younger in comparison to those treated between 2002 and 2011. This is an excellent example of improvement in AD treatment and dermatological management through the years. There were no statistically significant differences in the types of breaks observed between these two groups. This was in contrast to the AD and non-AD groups, where breaks were normally found in the peripheral ocular fundus in the former. Moreover, AD patients were younger and more prone to bilateral RD, macular or ciliary epithelium detachments than non-AD subjects. Interestingly, the rate of anatomical surgical success was not statistically significant in either the comparison of cases from 1991 to 2001 and 2002 to 2011 ($p > 0.4589$) or in the comparison of non-AD and AD individuals ($p > 0.2364$) [49]. Another retrospective study, also from Japan, analysed 417 eyes of AD patients with RD. A tendency towards breaks near the ora serrata was observed, as 63.8% of the examined eyes had breaks between the ora serrata and the equator and 19.7% exhibited breaks anteriorly to the ora serrata, while breaks in other locations were rare.

Table 1 presents data regarding the frequency of the most common type of retinal breaks experienced with RD in AD patients – oral dialysis.

Table 1. Frequency of the most common types of retinal breaks experienced with RD in AD patients – oral dialysis

Researcher	Frequency (%)
Hida <i>et al.</i> [44]	39.1
Takahashi <i>et al.</i> [46]	22.0
Sasoh <i>et al.</i> [49]	29.3

The most frequent surgery for retinal detachment in those eyes was scleral buckling (78.2%) [44]. Surgical management can be hindered by the fairly common presence of proliferative vitreoretinopathy (PVR) [50]. Flat retinal detachment is the most common type of RD observed in AD patients ($p < 0.01$) [51]. The same retrospective study estimated the frequency of RD in AD to be 19.2%. In a 2004 article, Lim and Chee identified the problem of the presence of flat retinal detachment being masked in patients with AD who have acute panuveitis with rapidly progressing cataract. More vigilance is therefore required in such cases [52].

Furthermore, we can suspect retinal detachment in individuals with AD when the pigmentation on the anterior eye chamber angle is moderate to dense. Such patients must have their fundus examined very carefully [53].

Cataract

Cataract in AD patients is usually bilateral, symmetrical and occurs in the posterior and anterior subcapsular regions [12, 15]. Its progression depends on factors such as eye rubbing and the severity of facial skin lesions [15]. Taniguchi *et al.* did not demonstrate a relationship between serum IgE levels, the duration of systemic or topical corticosteroid use (in the facial region) and cataract development [47]. However, Sasabe *et al.* proved an association between high serum IgE levels and cataract development in AD individuals [54]. A study of the Danish population revealed a correlation between cataract and AD only in patients younger than 50 years old [55]. Intraocular lens (IOL) subluxation may occur in some cases, due to eye rubbing following the procedure of cataract extraction and IOL implantation [50, 56].

Nevertheless, Garrity and Liesegang observed cataract and retinal detachment in 13.0% and 7.5% out of 200 patients with AD (ocular manifestations were observed in 42.5% of AD patients – 85 out of 200 examined) [11].

Glaucoma

Glaucoma and its relationship with AD is still underestimated and rarely described. The study of the Danish population mentioned above did not demonstrate a correlation between the two conditions [55]. However, Takakuwa *et al.* have proposed a new clinical term, atopic glaucoma, diagnosed when the vertical cup-disc ratio is > 0.7 and/or notching of the neuroretinal rim, compatible visual field loss, intraocular pressure (IOP) > 21 mm Hg, no correlation between IOP with glucocorticoid use and the presence of severe atopic dermatitis (affecting at least the face) are found [57]. The authors focused on patients with severe AD and advanced glaucoma without a history of using glucocorticosteroids in their study. They believe that this type of glaucoma is associated with proinflammatory factors and surgical treatment is frequently required due to high IOP [57].

Uveitis

A recent analysis (2012–2014) did not demonstrate a statistically significant correlation between the impact of atopy and the onset of uveitis ($p = 0.494$) [58].

The results of a case-control study by Hajdarbegovic *et al.* revealed a negative correlation between atopic eczema and occurrence of uveitis in sarcoidosis – 12% of individuals from the sarcoidosis uveitis group had AD in comparison with 26% of subjects from the control group ($p < 0.045$) [59]. The association may have an immunological explanation – active T helper type 1 cells (typical of sarcoidosis) may suppress the development of atopy (of which Th2 cells are characteristic) [60]. Nevertheless, one should consider the case of a 15-year-old boy with atopic erythroderma and bilateral cataract, unilateral keratoconus and iridocyclitis reported in the literature [9].

Children

Children constitute a specific group of patients for whom AD occurs more frequently in comparison to adults [4]. There are very few reports in the current literature regarding the coexistence of ocular manifestations and AD, and the reports which are available were published several years ago.

The rate of comorbidities (including ophthalmic complications) is reported to be significantly higher in infants with AD than in the control group (47% vs. 28%) [61]. Other sources estimate the frequency of ocular complications in AD to be approximately 16.7% [62]. In 59 children with AD studied by Carmi *et al.*, the following conditions were observed: nuclear cataract (1 case), papillofollicular conjunctivitis (11 cases), purulent bacterial conjunctivitis (1 case), chronic atopic blepharitis (1 case), and amblyopia (1 case). No severe ocular complications were observed. The probable causes of the latter might have been the young age of the patients or mild disease form according to the SCORAD index [19]. However, based on the study results, one cannot assume that serious ocular complications do not occur in paediatric patients. The case of an 8-year-old boy with AD who rapidly developed bilateral corneal hydrops proves this point [63]. The case demonstrates the rapidity of KC progression, where KC may develop within a very short period and, therefore, ophthalmological examinations should be performed not only frequently but also during the early stages of AD, particularly in children. One should remember that the earlier KC is diagnosed, the better is the chance for halting its progression with an appropriate cure. A French study concluded that all young, allergic boys with eye-rubbing tendencies and a recent onset of corneal astigmatism should be examined regularly in order for keratoconus to be detected at an early stage [64]. Studies demonstrating the relationship between AD and cataract in young individuals have also been published [65, 66]. The most frequent symptoms of AKC in paediatric

Table 2. The most serious ophthalmic complications in AD patients

Corneal hydrops [37, 63]
Infection after ophthalmic procedure [42, 43]
Retinal detachment [44, 49]
IOL subluxation [50, 56]

patients with atopy are conjunctival hyperemia and eczema (96%) [67].

Conclusions

To date, few articles concerning the correlation between AD and its ocular manifestations have been published. This is particularly true for the paediatric population, on whom very few studies have been conducted. Therefore, more research evaluating those relationships, in particular involving children, should be performed.

Individuals with atopic dermatitis should be examined by an ophthalmologist regularly, irrespective of the dermatological severity of AD, since serious ocular complications can occur despite even mild skin changes. Table 2 presents the most serious ophthalmic complications.

Children in particular should undergo an ophthalmological examination as soon as the diagnosis of AD is established, since ocular manifestations can progress rapidly and detecting them earlier will facilitate earlier diagnosis and appropriate treatment, so that permanent ocular damage can be prevented.

It is worth mentioning that we can not only detect some abnormalities but also prevent them by, *inter alia*, using antibiotics pre- and intra-operatively or administering proper AD treatment aimed at minimising itching and eye-rubbing, thereby reducing the future risk of a number of diseases such as keratoconus, retinal detachment, and cataract.

Conflict of interest

The authors declare no conflict of interest.

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