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REVIEW

Results of case-control studies support the association between contact lens use and *Acanthamoeba* keratitis

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Background: *Acanthamoeba* keratitis (AK) is ever more frequently reported in industrialized countries. The loss of the corneal surface integrity consequent to secondary microtrauma produced by the use of contact lens (CL) favors the penetration of the parasite into the corneal tissue.

Objectives: A scientific review was performed to investigate the association of CL wear as an *Acanthamoeba* keratitis (AK) risk factor.

Methods: A computerized screening of 7834 Medline articles (4623 from PubMed; 3211 from Scopus) used a strict selection criteria of case-control studies involving CL wear and/or trauma.

Results: The search yielded five case-control studies published from 1995 to 2012. All studies included showed a statistically significant positive association between AK and CL use, with a combined odds ratio (OR) of 10.21 (95%, confidence intervals [CI]; 3.57–27.64).

Statistical analysis: All studies included showed a statistically significant positive association between AK and CL use, though with differing OR values.

Conclusion: Though rare, AK should be held in higher consideration when ophthalmologists are faced with CL users exhibiting simplex-like lesions associated with circular stromal infiltrates and disproportionate ocular pain in respect to the objective clinical picture.

Keywords: keratitis, contact lens, *Acanthamoeba*

Introduction

Keratitis is an infective process of the cornea which may lead to serious visual impairments.[1] The microbiological etiology of the disease is varied and may be of viral, mycotic, or parasitic origin.[2]

Corneal parasitic infections, which were – up to recently – thought to be associated mostly with poor sociosanitary conditions, are ever more frequent in industrialized countries.[1,3–5]

Acanthamoeba (A) is a resistant protozoan often found in proximity to freshwater or saltwater sources, in swimming pools, thermal baths, air-conditioning filters, and in contact lens (CL) cleansing solutions.[6–8] The first observation of *Acanthamoeba* keratitis (AK) was reported by Nagington in 1974,[9] but it wasn't until 1975 that a causal relationship between AK and A was reported by Visvesvara et al.[10] The species of *Acanthamoeba* that produces the most serious forms of keratitis in humans are *Acanthamoeba castellanii, A. hatchetti, A. polyphaga, A. quina,* and *A. rhysodes.*[11]

Risk cofactors are particularly associated to the loss of the integrity of the corneal surface,[12] be it consequent to trauma or abrasions from an external contaminated

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object or a secondary microtrauma produced by the use of CL, which both favor the penetration of the parasite into the corneal tissue.[13] Moreover, even the exposure to environmental pollution could be associated to the developing of this keratitis, as reported by Lalitha et al.[14]

There are wide differences in the incidence of the condition around the world and over time, which include the changing CL solution market and local environmental issues, such as water storage and disinfection.

Nevertheless, KA is still a health problem that needs to be clearly faced, according to Ibrahim et al.[15]

The first phases of AK are characterized by fluctuating epithelial defects, epithelial opacity, pseudodendritis, and bulbar hyperaemia, symptoms which resemble the dendritic keratitis often seen with herpes simplex infection; and these symptoms produce intense eye pain.[16]

The evolution of the infection causes a stromal ulceration, lysis, and the characteristic circular and perineural infiltrates of the stroma as typical markers of AK. The diagnosis of this condition must be made quickly, because it is a potentially devastating condition which, if untreated, may return even after surgical intervention.[17]

Objectives

The aim of our study was to review the scientific literature regarding the association between CL use and AK, considering that the use of CL has become more widespread. We aimed to perform a pooled analysis of studies where the results could be combined. The main reason for this is to offer support for the development and communication of preventive strategies (technical brochures conveyed through territorial medicine and pharmacies), focused on implementing targeted educational programs among CL users. This awareness may help alert specialists about markers associated to an appropriate and early diagnosis of AK.

Methods

Identification of relevant studies

The Internet medical databases used for the search were PubMed and Scopus. On Medline and Scopus, we used the keywords "*Acanthamoeba* keratitis," "contact lens," "trauma," and "case control" linked by the Boolean operators and/or applying the following two algorithms:[3] "*Acanthamoeba* keratitis," and/or "contact lens," and/or "case-control study;"[6] and "*Acanthamoeba* keratitis" and/or "contact lens" and/or "microtrauma."

The identification of relevant studies was carried out within the time window from January 1995 to February 15, 2012, and was restricted to the English language. We only selected studies that clearly reported the following criteria – CL, trauma, and AK – that measured health outcomes on the basis of association measures (odds ratio [OR]). We excluded papers that did not meet these criteria.

Data extracted included first authors, publication year, nation, study design, sample size, OR of cases and controls, and 95% confidence intervals (CI).

Data extraction

To perform the review, we extracted data related to infection by *Acanthamoeba* keratitis in CL wearers. Extracted data regarded persistent infection, defined by the detection of ulcers in one or more consecutive medical control visits.

Statistical analysis

Pooled analysis was performed using the random-effects model, since heterogeneity was found between studies (P for homogeneity = 0.053). The pooled OR was calculated as the back-transformation of weighted mean of transformed ORs using DerSimonian–Laird weights.

Results

Identification of relevant studies

From Medline, we retrieved 7834 articles (4623 from PubMed and 3211 from Scopus). After sorting for duplicates, removing ineligible studies through PRISMA methods (Liberati et al[18]), and screening for titles and abstracts, we were left with twelve eligible full-text articles. Moreover, after a first analysis, seven of these full-text papers were excluded because of the lack of data regarding the association measures we were most interested in. This criteria led to a strict selection of sorted articles. PubMed is a highly sensitive search tool and retrieves many articles, although in a much less selective way. If the same article was found in more than one database, it was only used once. The eligible papers were obtained as full text.

The process of data extraction was performed by two independent researchers.

In the end, five studies were included in the systematic review (Figure 1). All studies were case-control studies published from 1995 to 2012.

The sample size ranged from 89 to 714 individuals. Three studies were published in the USA, one in Italy, and one in the UK. The characteristics of each study are shown in Table 1.

ORs ranged from 3.57 (95%, CI; 1.86–6.87), Verani et al,[19] to 27.64 (95%, CI; 6.46–135.54), Radford et al.[20] The five

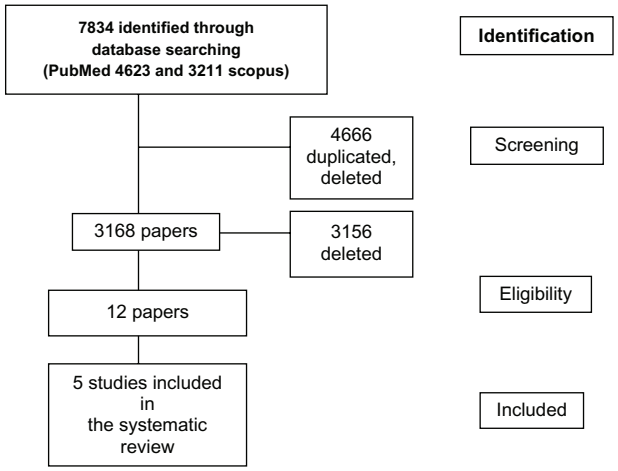

Figure 1 Flow diagram of AK studies selected.
Abbreviation: AK, *Acanthamoeba* keratitis.

selected studies analyzed all involved CL wearers who subsequently developed AK.

Statistical analysis

All studies included showed a statistically significant association between AK and CL use, though with different OR values: The study by Radford et al showed a statistically significant association with higher OR (OR = 27.64; 95%, CI; 6.46–135.54), while another three studies showed an association of more than 10 (Meier et al[21] [OR = 11; 95%, CI; 1.48–228.1], Joslin et al[22] [OR = 13.16; 95%, CI; 3.55–35.57], Pacella et al[23] [OR = 17.68; 95%, CI; 2.25–138.89]). In the remaining study, the OR value was less than 10 (Verani et al[19] [OR = 3.57; 95%, CI; 1.86–6.87]). Pooled OR scores produced a value of 10.21 (95%, CI; 4.01–25.99) and a *P* for homogeneity = 0.053.

Other relevant risk factors

According to the results from Joslin et al,[22] the reuse of solution more than five times per month is another CL significant risk factor for AK (at unconditional multivariate analysis OR = 4.20; 95%, CI; 1.25–14.10). Moreover, additional hygiene-related variables, such as lack of "rubbing" and showering with CL, as well as ocular trauma[22,23] may play an important role in the pathogenesis of this keratitis.

Discussion

This review takes into consideration five case-control studies published from 1995 to 2012, and in each study, a statistically significant positive association between AK and CL use was found. The strength of this work is that, for the first time, it summarizes a pooled measure of association (OR = 10.21).

Early diagnosis is certainly of primary importance for the prognosis and outcome of AK because of the devastating nature of this infection. All too often, pharmacological treatment does not produce effective results, and the condition may return even after surgical intervention.

The diagnosis of AK is based on an accurate anamnesis which is fundamental for the identification of probable associated risk factors. It relies on techniques such as confocal microscopy, which allows the examination of the human cornea in real time. This technique visualizes microorganisms present on the cornea and identifies them as highly reflective, oval, or circular bodies, with a diameter of 10 μm–25 μm. These organisms are then analyzed in the laboratory after swab specimens have been obtained by scraping the epithelium. The stroma specimens are obtained with the use of a Kimura spatula. The scraping of the cornea must always be carried out to obtain an epithelial and subepithelial culture coloration.[24]

The pharmacological treatment consists of an intense initial phase in which a combination of biguanide (propamidine isethionate 0.1% or chlorhexidine) and benzamidine (propamidine or pentamidine) is used to prevent the protozoan developing a chemical resistance. Subsequently, there was a maintenance period of variable duration, depending on the seriousness of the condition (which may even last up to 1 year).[22] In the most serious cases, inflammatory necrosis leads to the formation of corneal scars that require keratoplasty for the treatment of this perforation as part of the course of visual rehabilitation associated with anti-amoeba prophylaxis.[25,26]

Table 1 Results of case-control studies of keratitis caused by *Acanthamoeba* published from 1995 to 2012

Authors	Year	Nationality	Cases	Controls	OR	Lower 95% CI	Upper 95% CI
Radford CF et al[20]	1995	UK	12	378	27.64	6.46	135.54
Meier PA et al[21]	1998	USA	31	58	11	1.48	228.1
Joslin CE et al[22]	2007	USA	38	100	13.16	3.55	35.57
Verani JR et al[19]	2009	USA	72	140	3.57	1.86	6.87
Pacella E et al[23]	2012	Italy	11	703	17.68	2.25	138.89
Pooled data			164	1379	10.21	4.01	25.99

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

The number of cases recorded and described in the literature is notably on the increase,[16–20] and the aim of this study was to report the information pertinent to CL users and inform them about the diffusion and resistance of *Acanthamoeba* spp. in freshwater sources, including tap water.

A correct prevention envisages a scrupulous cleaning of CLs and their correct use, using ad hoc communication strategies that use the most efficient means of communication (information leaflets in pharmacies, doctor's waiting rooms, etc).[1,25]

Conclusion

Because of the disease's rare nature, it should be held in higher consideration when the ophthalmologist is faced with a CL user exhibiting simplex-like lesions associated with circular stromal infiltrates and disproportionate ocular pain in respect to the objective clinical picture. The temporal trend of publications has shown a steady increase from 1984 to the current time, testifying the interest in this rare disease among members of the international scientific community. In any case, we recommend that case-control studies need to be intensified to support risk evaluation, management, and communication better.

Disclosure

The authors report no conflicts of interest in this work.

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