INVolvEMENT OF THE EYE WITH Acanthamoeba

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ABSTRACT

Background/Aim: This review is based on the relevant literatures available in this subject. The aim is to give wide information about infection of the cornea by the parasite. Acanthamoeba causing acanthamoeba keratitis which is a potentially devastating corneal infection causing visual loss. The review gives emphasis on epidemiology, risk factors, clinical manifestations, pathogenesis, and management of the disease.

Conclusion: Acanthamoeba keratitis is a potential blinding infection of the cornea, it is essential to be early diagnosed, to avoid the risk of permanent visual impairment and blindness.

Keywords: Acanthamoeba, keratitis, Cornea, vision.

INTRODUCTION

Literally Acanthamoeba means spiny amoeba, Acanthamoeba are ubiquitous free-living protozoa that is found commonly in the environment, it has been reported in almost all parts of the world. Acanthamoeba infections may result in a granulomatous amoebic encephalitis (GAE), occurring mainly in chronically ill, debilitated patients. Wide variations in the incidence have been documented. Acanthamoeba keratitis can occur in patients of any age, sex or, race, but mostly manifests in young, healthy adults. Acanthamoeba keratitis occurs primarily in individuals who wear contact lenses however, it is possible for any one to develop this infection, Acanthamoeba keratitis is a potentially devastating corneal infection leading to visual loss.

Morphology and life cycle

Acanthamoeba exists in two stages in the life cycle:

1. The motile trophozoite 8-40 µm, with a single nucleus and a large dense, centrally located karyosome (nucleolus) (Fig 1) moves slowly with pseudopodia called "acanthopodia". The trophozoites are the infective form, although both trophozoites and cysts gain entry into the body.

2. The cyst stage is smaller and rounded 10-20 µm with double wall, a wrinkled outer wall (ectocyst) and polygonal inner wall (endocyst), it has a single nucleus, and the cysts do not exhibit any movements and may remain viable for many years until they are exposed to a food source where they gain assume the trophozoite form, Acanthamoeba are non-flagellated organisms.

Interestingly, it was reported that encystations of Acanthamoeba was inhibited by the serine proteinase inhibitor phenylmethanesulfonyl fluoride, it was shown that a serine proteinase is involved in mediating the encystation of Acanthamoeba (EMSP) and it was shown to be highly expressed during encystations by real time PCR and western blot analysis.

Epidemiology

Acanthamoeba spp. found commonly in nature, including, tap water, bottled water, swimming pools, hot tubs, contaminated water, lakes, rivers, thermal and brackish water, or in the sea. Soil, sewage system, cooling towers, heating, ventilation, Air conditioning system, Acanthamoeba have been isolated from solutions and cases of contact lens wearers.

In unfavorable surroundings, the trophozoite is turning into the cyst which can evade external conditions such as: Hyperosmolarity, glucose starvation, desiccation, extreme temperatures up to + 42 C° and extreme PH.

Manikandan et al analysed the prevalence, demography, predisposing factors and seasonal variations of Acanthamoeba keratitis. They concluded that Acanthamoeba keratitis is uncommon when the risk factors are absent and it is commonly seen among people who are exposed to Acanthamoeba through various predisposing factors. Knowledge of epidemiology and early diagnosis may prove vital for effective management of Acanthamoeba keratitis.

Pathogenesis of Acanthamoeba keratitis

The mechanisms associated with the pathogenesis of Acanthamoeba tends to be highly complex, depending on parasite, host and the enviromental factors.

Acanthamoeba likely invade the cornea through a physical opening such as minor
abrision, in the corneal epithelium. Contact lens wear may facilitate direct inoculation of *Acanthamoeba* into the eye and promote infection through the mechanical or hypoxic trauma to the cornea. Upon binding to mannose glycoprotein of the corneal epithelium, *Acanthamoeba* secretes proteases cytolytic to the epithelium as well as proteases that facilitate further penetration.

Amoeba bind to the corneal surface and produce corneal thinning and necrosis, eventually the parasites enter the stroma result in oedema, disruption of stromal lamellae and an intense polymorphonuclear response. IgA antibodies normally protect corneal epithelial cells from *Acanthameba* infection; however, certain *Acanthamoeba* spp are capable of producing proteases that lead to antibody degradation.

**Acanthamoeba keratitis**

Ocular infection by *Acanthamoeba* was first reported in 1973 in USA, since then hundreds of cases have been reported, a large number of which occurred in contact lens wearers. The disease can occur in non-contact lens wearers, nine cases of *Acanthamoeba keratitis* not associated with contact lens wear were diagnosed. A series from India of 39 non-contact lens wearing patients with *Acanthamoeba* were reported as well. *Acanthamoeba keratitis* in non-contact lens wearers was first reported among Egyptian patients, in addition, in South India, a 6-year epidemiological review indicated the increase prevalence of *Acanthamoeba keratitis* among non-contact lens users. In 2007, a three-year study in the same area in India revealed that the incidence of *Acanthamoeba keratitis* amongst the corneal ulcer patients was 1% and was mainly due to corneal infection by mud.

Eight of *Acanthamoeba* Species have been isolated as etiologic agents that cause ocular pathogenesis with *Acanthamoeba: A castellani, A polyphaga, A culbertsoni, A rhisodes, A griffini, A hatchetti, A quina, and A lugdunensis*. The diagnosis of *Acanthamoeba keratitis* in non-contact lens wearers is more difficult and often takes longer time, as the suspicion for the infection is usually lower.

**Risk factors:**

Contact lenses remain the most common risk factor for development of *Acanthamoeba keratitis*. All types of contact lenses were incriminated, Silicon hydrogen lens. The trophozoites attachment rates with these lenses were significantly higher than with conventional hydrogen lenses.

**Orthokeratology:**

The practice of orthokeratology in keratoconus, employing a rigid lens, alter corneal shape and providing temporary correction of corneal power has increased risk of *Acanthamoeba keratitis*. Recently, many cases and series have been reported in patients using orthokeratology.

As regard exposure to contaminated water another risk factor, culture from a patient who wore contact lenses for cosmetic reasons yielded *Acanthamoeba* spp. The amoeba isolated from the eye and hot tub was identical as *A. castellani*. The risk factors for *Acanthamoeba keratitis* have been studied in England and Wales, and revealed that the geographical variations in the incidence may be partly related to the increase risk associated with hard water. Detection of *Acanthamoeba* in tap water and contact lenses in Hong Kong was reported. Examination of soft contact lens solutions confirmed that *Acanthamoeba* responsible were to be found in the fluid.

In addition environmental conditions constitute an important risk factor, another risk factor is minor ocular trauma. Clinical manifestations

*Acanthamoeba keratitis*, present as unilateral, however, bilateral involvement has been described, it typically begins with foreign body sensation, severe pain, which is the whole mark of keratitis caused by *Acanthamoeba* which may be out of proportion to the apparent degree of corneal involvement, however, a case of *Acanthamoeba keratitis* reported, where the patient never complained of any pain. Other symptoms are eye redness, blurred vision, photophobia, conjunctival discharge. The clinical picture of *Acanthamoeba keratitis* is remarkable for its variation, *Acanthamoeba keratitis* can present initially as a dendritic keratitis, similar to herpetic, fungal, and or bacterial keratitis. A pattern of radial keratoneuritis (Fig 2), which is characterized by linear, radial branching infiltrate of the parasite along the corneal nerves into the anterior stroma is virtually pathognomonic. Other clinical signs of *Acanthamoeba keratitis* include:

Cornea with epithelial defects, corneal microcysts, bullous keratopathy, subepithelial infiltrate, anterior uveitis. More over, central corneal ulcer, also.

Additionally, *Acanthamoeba sclerokeratitis* in contact lens wearers; in whom scleritis (anterior and posterior) played a role in the clinical course of the disease. Chorioretinitis secondary to primary keratitis caused by *Acanthamoeba* has been reported.
A ring shaped stromal infiltrate (Fig 3) is characteristic of advanced infection and is pathognomonic. Keratoconus patients may have atypical presentation of acanthamoeba keratitis which may delay diagnosis and institution of medical therapy even brief use of topical anaesthetic may further complicate the clinical picture.

**Diagnosis**

Diagnosis of *Acanthamoeba keratitis* is difficult; the first important step is to suspect it, especially in contact lens wearers with the corneal involvement resembling herpes simplex keratitis presented with severe pain.

History: Suspicion should be increased with a history of ocular exposure to soil, contaminated water or a history of minor ocular trauma.

**Ocular Examination:**
- Visual acuity.
- Refractory test.
- Tear test.
- Slit lamp biomicroscopy examination.
- Pupillary reflex response.

**Laboratory diagnosis:**

- Scraping of the involved epithelium and stroma of the cornea vigorously with a sharpened Kimura spatula No 15.

- Culture of the organisms should be plated on non-nutrient agar with overlaid *Escherichia coli*, if the patient is a contact lens wearer, the lenses, lens case, and solutions should be cultured.

**Histopathological examination:**

*Acanthamoeba* have variable staining characteristics to demonstrate trophozoites and cysts of Acanthamoeba in samples from corneal smears, scrapings from cornea, biopsy (corneal button):
- Giemsa wright, (Fig 4) Gomori–methylene silver, Masson trichrome stain, Periodic acid Schiff (PAS), (3, 5, 28) 10% KOH wet mount preparation, (28, 36) Calcofluor white stain viewed with fluorescence microscope, where the cysts appear bright green, (38) Iron haematoxyline. (5, 25)

**Impression cytology:**

Impression cytology of *Acanthamoeba keratitis* with surface involvement to detect the cysts and trophozoites has been reported. It can be a usefull technique to facilitate early diagnosis of *Acanthamoeba keratitis* with surface involvement.

**Electron microscopy:**

- It has been used for identification of ultrastructures of the organisms and confirmation of diagnosis.

**Confocal microscopy:**

In vivo, confocal microscopy (IVCM) is a non-invasive imaging technique that provides high-resolution images of all the corneal layers.

*Corneal scrapings are independenty sensitive in detection of Acanthamoeba keratitis and a combination of both diagnostic modalities offers the highest likelihood of rapid and accurate diagnosis of Acanthamoeba keratitis in patients with atypical keratitis.*

**Indirect fluorescent antibody test (IFAT):**

It provides rapid and sensitive test for staining of corneal Scrapings.

**Immunoelectrophoresis (IEP):**

Analysis of protein extract of Acanthamoeba by IEP provides identification of separation of different isolates.

**Polymerase Chain Reaction (PCR):**

Polymerase Chain Reaction is the most sensitive and diagnostic method of *Acanthamoeba keratitis*, it is rapid, sensitive and require only a small amount of scrapings allowing early diagnosis.

Traditionally detection of trophozoites, cysts in cytological preparations or growth of *Acanthamoeba in culture* have been used to diagnose *Acanthamoeba keratitis*; however, conventional PCR has been found to be more sensitive, (7, 30) the validation of two real-time PCR have been established using the Cepheid SmartCycler 11 real-time PCR system.

**Molecular techniques:**

PCR amplification of the 18S ribosomal DNA proved to be sensitive method. Potentially able to detect *Acanthamoeba* without the need of long culture incubation, and thus considered usefull for clinical application. Genotyping work has focused on the 18SrRNA gene of *Acanthamoeba keratitis* as a basis for taxonomy of the genes. Tewelve images referred to as T1, T12 have been identified with the majority of keratitis causing strains belonging to group T4.

**Treatment**

1 - Medical treatment:

Unfortunately, *Acanthamoeba keratitis* does not respond to drugs. The main difficulty is resistance of *Acanthamoeba* cysts to antimicrobials.

Effective treatment began in the mid-1980s through the use of propamidine isethionate (Brolene) 0.1% (a 1% solution = 10 mg/ml), the authors reported the first successful medical control of *Acanthamoeba keratitis* with diamidine components, other reports are shown.

Significant progress in medical treatment of *Acanthamoeba keratitis* was not made until early 1990, with the introduction of Cationic antiseptic agents as: Biguanides: Polyhexa-
methylene biguanide (PHMB) and Chlorhexidine (CHX) 0.02% drops, hourly for 3 days, 2 hourly for weekly during subsequent weeks.

Antifungal drugs: as (imidazole derivatives), imidazole drops 1% solution proved effective against trophozoites but not cysts. Miconazole (topical) 1% clotrimazole (topical), itraconazole (systemic) 200 mg every day for 3 weeks and ketoconazolem (systemic). (45,75)

Aminoglycosides group: as Neomycin (ex neosporin or neomycin- polymyxin B-, gramicidin). The recommended triple medication therapy of Acanthamoeba keratitis should include cationic anticeptic agents, chlorhexidine or PHMB0.02% in combination with Broline 0.1% and neomycin). (45,75)

**Topical corticosteroids:**

Is controversial, it may inhibit neutrophils and macrophages in scavenging and destroying amoeba when used topically however,5,45,55 prescribed oral corticosteroids in order to reduce the subjective pain and reduce ocular immune response related inflammation.

**Surgical treatment**

In addition to its application in the advanced and complicated cases of Acanthamoeba keratitis it is reported to be applied in the development of secondary glaucoma which might occur as a result of angle closure mechanism, apparently without direct infiltration of the organism. (80)

Therapeutic Penetrating keratoplasty (TPK): Reports that recurrence of Acanthamoeba keratitis after (TPK) several months after the operation,4,6,8,9 other studies where the operation performed because a corneal perforation in a patient after failed corneal cross linking (CXL) when the bandage contact lens was contaminated.9,82 Complications of (TPK) are graft rejection, glaucoma and cataract.

Therapeutic deep lamellar keratoplasty (TDLK): It may be considered instead of TPK yielding similar graft survival, it was applied for medically unresponsive infectious keratitis,8,83 risk of disease recurrence. Prolonged use of topical antimicrobial agents is indicated prior to considering penetrating keratoplasty to give chance for cysts eradication. Use of postoperative prophylactic antiamoebics up to 1 year following surgery, should also be a strong consideration.

Phototherapeutic keratectomy (PTK) and deep lamellar keratoplasty (DLK): Were found to be effective surgical procedures especially in advanced Acanthamoeba keratitis that fails to respond to medical therapy and corneal debridment. (84)

**Amniotic membrane transplantation:**

Amniotic membrane transplantation is useful adjunctive surgical procedure for the management of infectious corneal ulcer and for treating corneal perforation by promoting wound healing and reducing inflammation. The technique may be good alternative to penetrating keratoplasty especially in acute cases in which graft rejection risk is high. (85,86,87)

**Prevention**

**Contact lens precautions:**

Contact lens wearers should be instructed to avoid the following:

Avoid swimming wearing contact lenses, showering with lenses, using a hot tub with lenses, coming in contact with contaminated water. (4,88) Patients should also be advised to wash their hands thoroughly before handling the lens, to avoid use of tap water, or saline on the lens, to clean and disinfect the lens on removal. To rinse the lens daily with saline or disinfecating solutions. (5,46) Hydrogen peroxide is reported to be effective in killing both trophozoites and cysts. (3,27)

The centers for disease control and prevention (CDC) in May 2007,89 issues a health advisory warning for contact lens wearers using Complete Moisture plus Multi - purpose contact lens solution (AMO) and the makers of AMO solution withdrew it from the market because of links to Acanthamoeba keratitis. Users of the product were advised by the federal officials to stop using the product immediately (the product is used to clean and store soft contact lenses, healing and reducing inflammation). The technique may be good alternative to penetrating keratoplasty especially in acute cases in which graft rejection risk is high.

In conclusion, Acanthamoeba keratitis continues to be difficult to diagnose and manage. The frequency of this infection may be on rise, and it is most commonly associated with frequent replacement of soft contact lens wear. Over night orthokeratology patients have also shown high rates of Acanthamoeba infection.

Delayed diagnosis or misdiagnosis and inappropriate anti microbial therapy results in poor visual outcome. So it is important for the ophthalmologists to consider it in patients especially in contact lens wearers with suspecting herpes simplex keratitis.
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الملخص العربي

إصابة القرنية بطفيل الأكانتامبيا

عملية حسن صفر

قسم الطفيليات – معهد بحوث أمراض العيون – الجيزة – القاهرة – مصر

يهدف هذا البحث المرجعي إلى تعريف الأصابة بطفيل الأكانتامبيا Acanthamoeba من حيث طرق العدوى، أعراض المرض، لتمكين اكتشافه مبكرًا للوقاية من الاصابة به، المحافظة على فعالية الإقصار. حيث تحدث الأصابة في القرنية العين وتحول أعراضها بانتشار زيادة الوعورة والحساسية الشديدة للتعرض للضوء والعالم في الحالات المتقدمة تظهر الالتهابات والتقرحات بالقرنية مما يؤدي إلى ضعف الإقصار ويمكن فقد الإقصار ومن أهم العوامل التي ينتج عنها المرض استخدام العدسات اللاصقة وتوليدها بمياه الملوثة أو استخدام محول الملح المحضر منزلياً أو مياه الصنبور لغسل العين. كذلك تعرض العين لزيادة الضغط.

تشخيص المرض: يتم التشخيص بعمل مسحة من ملتحمة العين أو القرنية أو المحول المستخدم في تنظيف العدسة اللاصقة ويتم زرع هذه العينات في مستنبات من مادة الأجزاء غير المغذى والمغذى بفطالة في البكتيريا ككولاي Escherishia coli ويتم فحصها بالميكروسكوب الضوئي كما يتم عمل شرايين صبغها، وبعض الخيوط المختلفة. كذلك يتم التشخيص باستخدام الميكروسكوب الافتوكليد لكشف الفصوص لرؤية الطور النشط أو الخيوط على الطبيعة في الأنسجة الحية. كذلك اتبارات مناعية أخرى. يتم العلاج بالأدوية أو جراحياً بعد ترفع للقرنية في الحالات المتقدمة.