• Investigation •

Resistant corneal ulcers in a tertiary care ophthalmic center in Egypt: 10 years epidemiological study

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Abstract

● **AIM:** To investigate the magnitude of problem caused by resistant corneal ulcers and its epidemiological characteristics.

● **METHODS:** Patients with corneal lesions were selected and carefully examined and cases with resistant corneal ulcers were further investigated and data were recorded using a specific data sheet designed in hospital. Then, collected data from patients were statistically analyzed.

● **RESULTS:** Totally 1939 cases were included in the study, including 816 fungal cases (42.1%) and 1123 (57.9%) non-fungal cases. Age of the participants ranged from 18 to 73y. Fungal cases were more common in middle age (35–55y). Men were more affected (53.5%) of cases included in the study. Keratomycosis affected more unskilled personnel (75.1%), large families with small houses (higher crowding index 73.9%), rural (64.5%) residence. Patients with sanitary water sources (34.8%) and waste disposal (24.4%) were less affected.

● **CONCLUSION:** Keratomycosis is more frequent in unskilled personnel, rural locations, outdoor water sources and insanitary waste disposal systems. Corneal trauma and contact lens are common risk factors.

● **KEYWORDS:** corneal ulcer; corneal lesion; corneal trauma; keratomycosis

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INTRODUCTION

Corneal ulcers represent a commonly-faced situation in ophthalmic care centers. It is a dangerous problem in non-developed world. Proper diagnosis represents a challenging situation in such cases. It should be based on both clinical characteristics of ulcers and laboratory investigations that confirm the possible clinical diagnosis or not[1-2].

Laboratory investigations that can revise clinical findings include culture and sensitivity of secretions and corneal scraping, pathological sections, corneal laser confocal microscopy and metagenomic next-generation sequencing (mNGS). In comparison with traditional laboratory methods, mNGS represents a promising method that provides a clue for diagnosis based on DNA detection of the possible causative organism and so it can be helpful in organism detection in cases with negative cultures[3-4].

Culture-based therapy doesn't achieve healing in many situations due to poor immunity, poor socioeconomic standards, lack of proper drugs, unavailable ophthalmic preparations, prolonged duration, and lack of specialized ophthalmologist in distant locations[5-6]. Consequently, a remarkable percentage of such cases of keratitis worsen over course of treatment and so adjunctive interventional maneuvers are tried to improve healing[7].

Intra-stromal injection was adopted as effective approach for resistant keratitis[8]. Transplantation of human amniotic membrane (AM) is also tried to enhance improvement because it has anti-bacterial, anti-angiogenic, anti-inflammatory and anti-fibroblastic properties[9]. Surgical debridement to allow drug penetration is also tried to give a space for quicker healing[10]. Argon laser irradiation of corneal tissue produces thermal damage and coagulation of proteins that help organism destruction and corneal tissue strengthening to enhance healing[11].

Due to lack of comprehensive studies that discuss the magnitude and report the epidemiological features of the problem caused by resistant corneal ulcers in Egypt, it was believed that a study that investigate such problem was so valuable. This problem is also affected by the fact that Egypt is a one of the middle east countries with large number of population and specific geographical characteristics like the river Nile and surrounding deserts. Other factors like socioeconomic level, educational background and health services availability greatly participate in that problem.

Those specific criteria affect the problem in Egypt and give peculiarity that differs from other regions in the world.

PARTICIPANTS AND METHODS

Ethical Approval The study was designed as retrospective study including data collected from 1/1/2014 to 31/12/2023 at Cornea Clinic in Tanta University Hospital. Ethical committee approval code: 36264PR459/12/23. The study was conducted in accordance with the principles of the Declaration of Helsinki. The informed consent was obtained from the participants.

Corneal lesions were selected to include those cases suffering from corneal ulcers which were refractory to medical therapy for more than 7d despite treatment given outside our center before the first visit and did not achieve healing nor improvement. And so those cases were considered resistant corneal ulcers and consequently included in our study. All cases were submitted to ophthalmological examination, ocular ultrasonography and slit lamp photography for documentation.

Clinical diagnosis of the possible invading organism was done depending on the presence or absence of multiple clinical signs like size and shape of ulcer, corneal edema, area of infiltration, satellite lesions, feathery edge of infiltration and hypopyon then confirmation of diagnosis was done by culture and sensitivity testing.

Cases were randomly divided into 2 groups: fungal keratitis and non-fungal keratitis groups.

A data sheet was designed and filled by the researchers.

1) Sociodemographic characteristics: age and sex; occupation: unskilled personnel (jobs that don't need education like farmers and manual workers), skilled personnel (jobs that need a level of education like electrician, plumber and carpenter) or housewives; family size (number of family members); crowding index number of family members to number of rooms per residence); residence (rural or urban); water supply (pipes or underground pump); waste disposal (pipes or conservancy).

2) History taking to: previous drug therapy specially antibiotics, corticosteroids and immune-suppressants; corneal trauma (mechanical, physical or chemical insults specially plant trauma); co-existing systemic diseases (diabetes mellitus, tuberculosis, hepatic disorders, renal impairment and cancer); previous ocular surgery; local eye diseases as dryness and glaucoma; the time of onset of present condition till first visit; history of recurrence.

3) Laboratory investigations: culture and sensitivity: with surface anesthesia, edge and bed of the ulcer were scraped to obtain enough sample for microbiological work-up including direct stained smear and culture isolation to detect offending organism. Basically Sabouraud dextrose agar was used. Preparation of media plates was done using 0.05% chloramphenicol, then autoclaving was done to ensure sterilization and finally spread on Petri dishes. When fungal growth was identified after inoculation and incubation, the sensitivity tests were done *in vitro* using specified antifungal agents. Microbial isolates showed susceptibility to many antifungal drugs including fluconazole, voriconazole, itraconazole, natamycin, and amphotericin B. Regarding susceptibility to antibiotics, isolates (cases with mixed infection both fungal and bacterial) were susceptible to moxifloxacin, gatifloxacin, ciprofloxacin, ofloxacin, tobramycin and amikacin. These drugs were used as ready-made eye drops or prepared as fortified drops with specific concentration according to availability of eye drops.

Treatment was prescribed according to culture and sensitivity findings and continued till achieving healing. In some instances, failure of healing happened and further adjunctive measures were needed to allow improvement and give a chance for healing like: surgical corneal debridement; intra-stromal injection; AM transplantation; argon laser photocoagulation; cyanoacrylate glue; combination of more than one of the above measures; tectonic or therapeutic keratoplasty.

Statistical Analysis The collected data were coded and analyzed using the Statistical Package for Social Sciences (SPSS) version 22 for Windows® (SPSS Inc, Chicago, IL, USA). The data were presented as mean, standard deviation, frequency, and percentage as appropriate. *P* value of 0.05 or less was considered significant.

RESULTS

Our study included 1939 cases. Patients with pure fungal growth, mixed (fungal and bacterial) growth or clinical findings of mycotic keratitis despite negative culture constitute 816 cases (42.1%). Other cases were considered non-fingal (1123 cases representing 57.9%).

Right eye was involved in 687 cases (35.4%) and left eye in 1252 cases (64.6%). The 1792 patients (92.4%) developed hypopyon (1–8 mm). Corneal lesions measured 2–8 mm with mean of 4.98±1.13 mm.

The participants aged 18–73y. The mean age of patients with fungal contamination was 43±3.12y while patients with no fungal contamination was 45±2.78. Table 1 showed that patients aged less than 35y represented 239 (29.3%), from 35 to 55y represented 396 (48.5%) and more than 55y represented 181 (22.2%) in fungal group. The same age categories in the non-fungal group recorded 334 (29.7%), 553 (49.2%), and 236 (21.1%) respectively. Insignificant difference was detected (χ^2=0.381, *P*=0.827).

In fungal group, males represented 420 (51.5%) and females represented 396 (49.5%) cases while in non-fungal group, males represented 617 (54.9%) and females represented 506 (45.1%) cases. Statistical analysis showed insignificant difference (χ^2=2.29, *P*=0.13).

The major percentage was unskilled personnel in both groups: 613 (75.1%) in fungal group and 702 (62.5%) in non-fungal group. Skilled personnel constituted 6.1% of fungal group cases while 20.3% of the non-fungal group cases. The 18.8% of cases were housewives in fungal group while 17.2% of cases of non-fungal group were housewives (Table 2). Statistically significant difference was detected (χ^2=77.97, *P*=0.00001).

Most of cases of resistant keratitis are from large-sized families with small houses; fungal cases from families with more than 4 members recorded 503 cases (61.6%) where non-fungal cases of the same category recorded 736 cases (65.5%). High crowding index was recorded 603 (73.9%) and 866 (77.1%) in both groups respectively (Table 3). The difference was statistically insignificant for both family size (χ^2=3.11, *P*=0.0778) and crowding index (χ^2=2.66, *P*=0.103).

Most of fungal cases were from rural areas 526 (64.5%). The same for non-fungal cases 682 (60.7%). Unsafe water supply (underground pump) was found in 532 (65.2%) cases in fungal group while 725 (64.6%) cases in non-fungal group. Insanitary waste disposal system (conservancy) was found in 617 (75.6%) cases in fungal group while in 704 (62.7%) cases in non-fungal group as shown in Table 4. The difference was not statistically significant in case of residence (χ^2=2.8, *P*=0.942) and in case of water supply (χ^2=0.084, *P*=0.772) while it was significant in case of waste disposal (χ^2=36.35, *P*=0.00001).

Most common risk factor in fungal group was corneal trauma: 286 cases (35%) while in non-fungal cases was contact lens use: 351 cases (31.3%). More than one risk factor was detected in 186 fungal cases (22.8%) while in 263 non-fungal cases (23.4%). No detected risk factors were found in 23 fungal cases (2.8%) while 43 non-fungal cases (3.8%) showed no obvious risk factors. Recurrence was detected in 61 (7.5%) cases in fungal group while 83 (7.4%) cases in non-fungal group (Table 5).

Aspergillus flavus was the most common fungus isolate detected by culture in 317 cases (38.8%). *Aspergillus niger* came second in 216 cases (26.5%). The 183 cases (22.4%) were caused by *Candida albicans. Mucor racemosus* was the least frequent fungus isolate in 29 cases (3.6%). Multiple fungus isolates were detected in the same patient in 113 cases (13.8%). No obvious fungal isolates were detected in 79 cases despite clinical findings of mycotic keratitis (9.7%) as shown in Table 6.

Healing results were: 488 (59.8%) cases healed with medical therapy alone, 311 (38.1%) cases needed adjunctive measures and 17 (2.1%) cases ended with endophthalmitis (Figure 1) in fungal group. In non-fungal group, healing results were 723 (64.4%), 368 (32.8%), and 32 (2.8%) cases respectively with statistically significant difference (χ^2=6.54, *P*=0.038).

Table 1 Age distribution between both groups *n* (%)

Age	Fungal	Non-fungal	χ^2	*P*
Less than 35y	239 (29.3)	334 (29.7)	0.381	0.827
35–55y	396 (48.5)	553 (49.2)		
More than 55y	181 (22.2)	236 (21.1)		
Total	816	1123		

χ^2: Chi-square test.

Table 2 Occupation of both groups *n* (%)

Occupation	Fungal	Non-fungal	χ^2	*P*
Skilled personnel	50 (6.1)	228 (20.3)	77.97	0.00001[a]
Unskilled personnel	613 (75.1)	702 (62.5)		
Housewives	153 (18.8)	193 (17.2)		
Total	816	1123		

χ^2: Chi-square test; [a]Significant.

Table 3 Family size and crowding index among fungal and non-fungal groups *n* (%)

Parameters	Fungal	Non-fungal	χ^2	*P*
Family size			3.11	0.0778
Less than 4 members	313 (38.4)	387 (34.5)		
More than 4 members	503 (61.6)	736 (65.5)		
Crowding index			2.66	0.103
<2	213 (26.1)	257 (22.9)		
>2	603 (73.9)	866 (77.1)		
Total	816	1123		

χ^2: Chi-square test.

Table 4 Residence, water source, and waste disposal system in both groups *n* (%)

Parameters	Fungal	Non-fungal	χ^2	*P*
Residence			2.8	0.942
Urban	290 (35.5)	441 (39.3)		
Rural	526 (64.5)	682 (60.7)		
Water source			0.084	0.772
Closed pipe	284 (34.8)	398 (35.4)		
Underground pump	532 (65.2)	725 (64.6)		
Waste disposal system			36.35	0.00001[a]
Closed pipe	199 (24.4)	419 (37.3)		
Conservancy	617 (75.6)	704 (62.7)		
Total	816	1123		

χ^2: Chi-square test; [a]Significant.

Table 5 Risk factors detected in fungal and non-fungal groups *n* (%)

Risk factors	Fungal	Non-fungal
Corneal trauma	286 (35)	324 (28.9)
Contact lens use	214 (26.2)	351 (31.3)
Systemic diseases	191 (23.4)	294 (26.2)
Previous ocular surgery	126 (15.4)	273 (24.3)
Prolonged use of antibiotics	72 (8.8)	107 (9.5)
Immune suppression	96 (11.8)	113 (10.1)
More than one factor	186 (22.8)	263 (23.4)
No detected factor	23 (2.8)	43 (3.8)

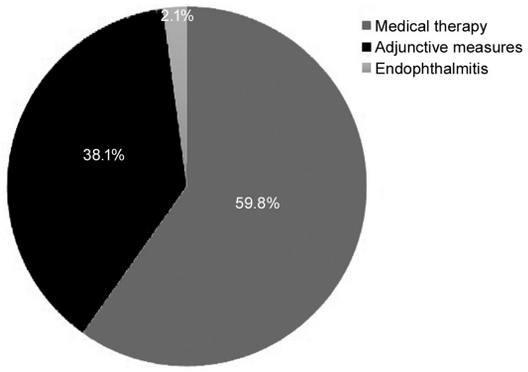

Figure 1 Fate of cases of resistant fungal corneal ulcers.

Table 6 Type of fungus isolates detected by cultures *n* (%)

Type of fungal infection	No. of cases
Aspergillus flavus	317 (38.8)
Aspergillus niger	216 (26.5)
Candida albicans	183 (22.4)
Penicillium lanosum	62 (7.6)
Fusarium oxysporum	44 (5.4)
Mucor racemosus	29 (3.6)
More than one species	113 (13.8)
Negative culture	79 (9.7)

DISCUSSION

Resistant keratitis causes blindness all over the world especially in less developed countries. It accounts for half of cases of corneal opacification causing profound visual insult. The world health organization exerts many efforts to protect people from such serious disease and prevent blindness[12-13].

There were insignificant differences between the two groups regarding most of variables like age, sex, and residence indicating proper randomization and nullifying any bias that skewed the results in favor of one group.

We concluded that age category (35 to 55y) was the most affected in both groups. It accounts for about half of cases included in this study. Males are more prone to resistant corneal ulcers (more than 50%) in both groups. These findings come in agreement with the study done by Ting *et al*[14] summarized literature published (2010 to 2020) and categorized those reports into six distinct regions. They concluded that infectious keratitis is more common in age group (30–55y) and affecting males more than females due to higher rates of exposure to environmental trauma which is a high risk factor to resistant keratitis.

Unskilled personnel (mainly farmers and manual workers) accounted for 75.1% of cases in fungal and 62.5% in non-fungal groups. Housewives came second in both groups. These findings may be attributed to poor socioeconomic standard and liability to trauma (35%) and contact lens use (26.2%) with poor personal hygiene that constitute most common 2 risk factors for mycotic keratitis. Our results are similar to those found by Mahmoudi *et al*[15] published in 2018 that found 40%–60% of fungal keratitis are due to vegetative trauma in agricultural areas and about 60% of cases in more developed countries. In 2021 in Indian study done by Rai *et al*[16], they concluded that fungi are responsible for a wide variety of infections including mycotic keratitis causing blindness, particularly in tropical and subtropical countries. It is more common in workers in outdoor environment. Moreover, trauma is the most important predisposing cause of mycotic keratitis. In hospital-based study done by Nath *et al*[17], 310 consecutive corneal ulcer cases seeking ophthalmic care services at Assam Medical College were enrolled. They confirmed that farmers are at high risk of fungal resistant keratitis especially after trauma of plant origin. Stapleton *et al*[18] reported that infectious keratitis is rare but severe condition associated with a range of ocular and systemic predisposing conditions, including ocular trauma, surface disease, and contact lens wear.

We recorded that patients of both groups belong to large families with high number of members (more than 4 members accounts for about 2 thirds of cases of both groups) and live in relatively small houses with little number of rooms and consequently high crowding index (about 3 quarters of cases of both groups) and crowding index. Those findings can be explained by the fact that large families with small houses suffer from poor health education, improper personal hygiene, over-crowdedness, poor ventilation and insanitary environment that increase the liability for many diseases including resistant corneal ulcers especially in rural areas.

We found an interesting conclusion that closed pipe systems for both water supply and waste disposal represent a great protection against infectious diseases notably resistant keratitis due to proper sanitation that decreases the liability of transmission of infecting microorganisms. Unsafe water sources accounted for about 2 thirds of cases in both groups while insanitary waste disposal accounted for 3 quarters of fungal cases while only 2 thirds of non-fungal cases. Many previous reports confirmed those findings. Prajna *et al*[19] at Aravind Eye Hospital in India in 2017 confirmed that fungal keratitis is more prevalent in rural locations with poor socioeconomic standards. Brown *et al*[20] discussed the fungal keratitis diagnostic literature and estimated the global burden through a complete systematic review from 1946 to 2019. They reported that insanitary water and waste disposal systems are common risk factors for fungal keratitis.

Our study reported that more than 2 thirds of cases were caused by *Aspergillus* species especially *flavus* (38.8%) and *niger* (26.5%) then came in the second place *Candida albicans* accounting for about one fifth of cases. These results are similar to the findings reported by many researchers. Mahmoudi *et al*[15] reported that *Aspergillus* species are highly contaminating

fungi in tropical and subtropical regions. Chi *et al*[21] reported in the study conducted in China in 2023 that *Aspergillus* species are main fungal pathogens in fungal keratitis and are responsible for many cases. Indian population-based study done by Maharana *et al*[22] confirmed that *Aspergillus* species are common organisms implicated in mycotic keratitis because they are saprobes that invade traumatized or immunologically compromised corneas. In a study included 500 cases of fungal keratitis who attended Cornea services at Aravind Eye Hospital in India, the researchers found that 52.5% of cases were caused by *Fusarium* species while *Aspergillus* species accounted for only 16.3% of cases[23]. Prevalence of *Aspergillus* species in specimens obtained from fungal keratitis can be attributed to the massive environmental spread of that organism especially its spore form which is highly resistant to cruel conditions like desiccation and hot climate so can survive.

We found that about 10% of cases of fungal corneal ulcers were culture-free despite fungal clinical findings and response to antifungal agents. This may be explained by superficial specimen or single area sampling. Negative cultures of mycotic keratitis represent a relatively common issue in the previous reports[24].

Culture-based medical therapy is the first strategy used in our study for all cases. About 2 thirds of cases [fungal 488 (59.8%) and non-fungal 723 (64.4%)] included responded but with different durations according to organism, and immunity of patient. The remaining third needed further maneuvers like corneal debridement, intrastromal drug injection and argon laser photocoagulation or combination of more than one maneuver to accelerate healing and promote closure of corneal defect. Many previous reports showed promising results of such maneuvers[8-11,25].

Study Limitations Lack of coverage of all regions of Egypt because it is a single-center study. Another limitation that during the period of time passed between the beginning of the disease and the first visit to our tertiary center many data cannot be collected due to unavailability of records

In conclusion, resistant keratomycosis constitutes major percentage of resistant keratitis. They are more frequent in middle age and unskilled personnel especially males. It is more common in rural locations with crowded houses. It is favored by insanitation. Plant trauma and contact lens are common risk factors. So we should improve society health knowledge and enhance environmental conditions to compete risks of resistant corneal ulcers. Also healthcare services should be improved and provided on a larger scale to give a chance to get better visual results and prognosis.

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