Original Article

Frequency and visual outcomes of herpes simplex keratitis in a Kuwaiti tertiary referral center

Nancy M. Lotfy [1], Nora Aldhefeery [2], Mariam N. Alenezi [2], Yousuf Alherz [2] and Yousef Taleb Ali [2]

[1] *Department of Ophthalmology, Kasr Alainy Faculty of Medicin, Cairo University, Cairo, Egypt*
[2] *Department of Ophthalmology, Farwaniya Hospital, Kuwait*

ABSTRACT

Background: Herpes simplex virus (HSV), a cause of many ocular pathologies, may affect the corneal epithelium, stroma, or endothelium, with the epithelium as the most frequently affected location. We aimed to determine the frequency and visual outcomes of HSV keratitis over a 1-year period at Farwaniya Hospital, Kuwait.

Methods: This prospective observational case series included patients diagnosed with HSV keratitis who presented to the outpatient or eye casualty department between September 2022 and September 2023. Full history, demographic profile, detailed ocular and slit-lamp examinations, and visual acuity assessments were recorded prior to and after treatment. Baseline corneal sensation was assessed in the four corneal quadrants using the cotton wisp test.

Results: Of the 227 patients who presented with infectious keratitis, 72 (31.7%) were diagnosed with HSV keratitis. The mean (SD) age was 45.86 (16.06) years, and 48 (66.7%) patients were male. The subtypes of HSV keratitis were endotheliitis in 27 (37.5%) patients, dendritic ulcer in 22 (30.6%), stromal keratitis with ulceration in 9 (12.5%) and without ulceration in 8 (11.1%), and geographic ulcer in 6 (8.3%). The mean baseline best-corrected distance visual acuity (BCDVA) differed significantly between the HSV keratitis subtypes ($P < 0.001$). Most patients (n = 70, 97.2%) had unilateral eye involvement, were treated within 1 – 2 weeks, and demonstrated improved BCDVA. Despite the improvement in BCDVA in all HSV keratitis subtypes, a significant difference in the median BCDVA remained after treatment ($P < 0.001$). Pairwise comparisons revealed a significantly better BCDVA after treatment in eyes with dendritic epithelial ulcers than in eyes with HSV stromal keratitis with ulceration ($P = 0.003$) or geographic epithelial ulcers ($P = 0.005$). After treatment, corneal haze and neovascularization were detected in 54 (75.0%) and 24 (33.3%) patients, respectively.

Conclusions: We detected a substantial frequency of HSV keratitis in one of the governorates of Kuwait, with endotheliitis as the most common manifestation. Timely standard treatment interventions based on valid guidelines resulted in BCDVA improvement in all subtypes of HSV keratitis in our series, indicating the importance of early treatment. However, the BCDVA in eyes with dendritic epithelial ulcers remained substantially better than that in eyes with geographic epithelial ulcers or HSV stromal keratitis with ulceration, signifying the effect of the initial HSV keratitis subtype on visual outcomes. To our knowledge, this is the first study to highlight the frequency of HSV keratitis in a Kuwaiti hospital, and larger-scale research in this region is needed to further understand and manage the condition.

KEYWORDS

herpes simplex virus infection, herpetic keratitis, social epidemiology, frequency, Kuwait, Zovirax, acyclovir sodium

Correspondence: Nancy M. Lotfy, Department of Ophthalmology, Kasr Alainy Faculty of Medicin, Cairo University, Cairo, Egypt. Email: nancymaher@kasralainy.edu.eg. ORCID iD: https://orcid.org/0000-0002-9159-0020

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INTRODUCTION

Herpes simplex virus (HSV), a cause of many ocular pathologies, may affect the corneal epithelium, stroma, or endothelium [1], with the epithelium as the most frequently affected location [2]. In the developed world, HSV keratitis is the most common infectious cause of corneal blindness, which is a result of stromal opacification [3].

HSV type 1 (HSV-1) is the more common causative strain [4], whereas HSV type 2 (HSV-2) typically manifests in neonates of infected mothers [5]. When HSV-1 is latent within the trigeminal ganglion, acute infection may be triggered by several factors such as trauma, emotional or psychological stress, and menstruation, but not been proven by the Herpetic Eye Disease Study Group [1, 6]. Recent studies have shown associations with intravitreal or botulinum toxin injections and after cataract or corneal procedures [1, 7, 8].

HSV keratitis usually presents with epithelial dendritic patterns, which may be branching or non-branching. Ulcers may also develop in many forms, leading to inflammation of the cornea and its layers, which consequently affects corneal innervation and may cause corneal thinning, perforation, and scarring [1, 2]. According to the American Academy of Ophthalmology, HSV keratitis can be classified as epithelial keratitis (dendritic or geographic ulcer), stromal keratitis without ulceration (non-necrotizing, interstitial, or immune keratitis), stromal keratitis with ulceration (necrotizing keratitis), or endotheliitis (disciform keratitis) [9].

Globally, an estimated 4.85 billion people are infected with HSV-1 [10], with 1.5 million new HSV keratitis cases each year. Of these, approximately 40 000 have severe monocular visual impairment or blindness, and disease rates are possibly higher in the developing world [3]. In the USA, approximately 50% of HSV-1 cases occur before the age of 30 years, and all individuals aged ≥ 60 years have latent HSV-1 in the trigeminal ganglion [1]. By contrast, approximately 90% of Africans (in certain continental regions) develop HSV-1 keratitis by adulthood [2]. The same percentage was found in developing countries in Latin America [11], indicating a stark contrast between developed and developing societies. Research on this topic has mostly been conducted in Western countries, leaving a knowledge gap in most parts of the world, including Kuwait and other Gulf Coast Countries (GCC) [12], where there has been little to no research on the prevalence of herpetic keratitis [13].

In this study, we investigated the frequency and treatment outcomes of HSV keratitis at Farwaniya Hospital in Kuwait. Limiting our study to the GCC population, our results may provide valuable insight into our regional disease burden.

METHODS

This prospective observational case series recruited all patients with any subtype of HSV keratitis who visited the outpatient or eye casualty department of Farwaniya Hospital, Kuwait, between September 2022 and September 2023. All patients had progress reports documented in their medical records up to the completion of a standardized treatment protocol. The total number of patients with infectious keratitis who visited the hospital during the study period was also recorded. This study was approved by the Medical Ethics Committee of the Kuwait Ministry of Health. The study protocol was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

The clinical classification of HSV keratitis is based on the corneal site and anatomical localization. In this study, we used the following classification [9]: 1) Epithelial keratitis: a) dendritic epithelial ulcers (lesions with branching, linear pattern with terminal bulbs) [14]), and b) geographic epithelial ulcers (broad ulcers with swollen, scalloped, or geographic epithelial borders) [14]); 2) Stromal keratitis: a) stromal keratitis without ulceration (non-necrotizing, interstitial, or immune stromal), and b) stromal keratitis with ulceration (necrotizing) [9]; and 3) endothelial keratitis or endotheliitis (disciform) [9].

The presence of corneal vascularization and haze after treatment were graded with scores ranging from 0 to 3 [15]. Regarding vascularization, 0 = no evidence of corneal vascularization, 1 = presence in one quadrant, 2 = presence in two quadrants, and 3 = presence in three or more quadrants. Regarding corneal haze, 0 = none, 1 = mild (iris details clearly visible), 2 = moderate (iris details not clearly visible), and 3 = severe corneal haze / opacification (anterior chamber structures not visible) [15].

We documented the full ophthalmic history and demographic profile (sex, age, and nationality) of each patient. All patients underwent a detailed ocular examination including a comprehensive anterior segment slit-lamp examination (Haag-Streit Photo-Slit Lamp BX 900; Haag-Streit, Koeniz, Switzerland); posterior segment assessment under slit-lamp using a + 90 D auxiliary lens (Volk Optical Inc., Mentor, OH, USA) if media did not preclude an adequate view of the posterior segment; measurement of best-corrected distance visual acuity (BCDVA) and uncorrected distance visual acuity (UCDVA) using a Snellen chart (Auto Chart Projector CP 670; Nidek Co., Ltd., Gamagori, Japan); intraocular pressure measurement (Applanation Tonometer 900;

Haag-Streit); corneal sensation assessment [16] in the four corneal quadrants using the cotton wisp test [17]; and in certain cases, corneal scraping for culture and antimicrobial sensitivity testing [18].

In five cases of atypical keratitis, corneal scraping for culture and antimicrobial sensitivity was performed [18] to rule out fungal or bacterial causes. Initially, a preservative-free topical anesthetic (MINIMS® oxybuprocaine hydrochloride 0.4%; Bausch & Lomb, NY, USA) was applied. Corneal tissue scrapings were then obtained using a disposable No. 11 scalpel blade, and a thin smear of tissue was placed on two glass slides for microbiological examination. Additional scrapings were then taken and applied to culture media, including blood agar, chocolate agar, and Sabouraud dextrose agar [19, 20].

In this study, we followed the HSV keratitis treatment guidelines reviewed and accepted by the Hoskins Center for Quality Eye Care, American Academy of Ophthalmology, in the June 2014 Compendium of Evidence-Based Eye Care [21]. Patients were regularly re-examined after the initiation of treatment and assessed for treatment-related local or systemic adverse reactions. BCDVA and the presence of corneal neovascularization or haze were recorded after treatment completion.

Analyses were conducted using the Statistical Package for the Social Sciences software (version 26; SPSS Inc., IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies and percentages. Age is presented as the mean and standard deviation (SD) owing to the normality of data distribution according to the Shapiro – Wilk test. BCDVA data at baseline and after treatment were converted to logarithm of the minimum angle of resolution (logMAR) values. Baseline BCDVA values were normally distributed and are presented as means and SDs. The variances were evaluated for homogeneity and were found to be homogeneous ($P = 0.131$). One-way analysis of variance (ANOVA) was used to assess differences in the mean BCDVA values at presentation between the subtypes of HSV keratitis. Post hoc multivariable comparisons were performed using the Dunn – Bonferroni test [22]. BCDVA values after treatment were not normally distributed according to the Shapiro – Wilk test ($P < 0.001$) and are presented as medians and interquartile ranges (IQRs). The Kruskal – Wallis test was used to determine post-treatment differences in the median BCDVA values between the subtypes of HSV keratitis. The Dunn – Bonferroni test [22] was used for pairwise comparisons of the median post-treatment BCDVA values between the HSV keratitis subtypes. The statistical significance level for all association analyses was set at $P < 0.05$.

RESULTS

Of the 227 patients with infectious keratitis who presented to Farwaniya Hospital within 1 year, 72 (31.7%) were diagnosed with HSV keratitis Five patients with atypical stromal keratitis underwent corneal scraping, and cultures yielded negative results for both bacterial and fungal infections. Table 1 lists the socio-demographic data of the 72 patients. The mean (SD) age was 45.86 (16.06) years, and 48 (66.7%) patients were male ($P = 0.846$). More than two-thirds of the patients were non-Kuwaiti (n = 49, 68.1%), whereas Kuwaitis represented approximately one third (n = 23, 31.9%) (Table 1).

Most patients (n = 70, 97.2%) had unilateral eye involvement, with 42 (58.3%) in the right eye and 28 (38.9%) in the left eye; only two patients (2.8%) had bilateral involvement. Decreased corneal sensation was detected in 60 (83.3%) patients. Endotheliitis was the most common subtype of HSV keratitis (n = 27, 37.5%), followed by dendritic epithelial ulcer (n = 22, 30.6%) (Table 1).

Table 2 summarizes the BCDVA values for the HSV keratitis subtypes before and after treatment. An ANOVA P value < 0.001 indicated significant differences in the mean BCDVA values between the different subtypes of HSV keratitis at the time of presentation. Pairwise comparisons revealed statistically significant differences in mean BCDVA on presentation between eyes with dendritic epithelial ulcers and geographic epithelial ulcers ($P = 0.017$), eyes with dendritic epithelial ulcers and HSV stromal keratitis with ulceration ($P < 0.001$), eyes with HSV stromal keratitis with ulceration and HSV stromal keratitis without ulceration ($P = 0.001$), and eyes with endotheliitis and HSV stromal keratitis with ulceration ($P < 0.001$).

BCDVA after treatment is summarized in Table 2 as the median (IQR) for each subtype of HSV keratitis. A Kruskal – Wallis P value < 0.001 revealed significant differences in the median BCDVA values after treatment among the different HSV keratitis subtypes ($P < 0.001$). Pairwise comparisons revealed statistically significant differences in the median BCDVA values after treatment between eyes with dendritic epithelial ulcers and HSV stromal keratitis with ulceration ($P = 0.003$) and between eyes with dendritic epithelial ulcers and geographic epithelial ulcers ($P = 0.005$). The follow-up durations in weeks are summarized in Table 2 as median (IQR) for all and each subtype of HSV keratitis.

Most patients (n = 60, 83.3%) were treated within 1 – 2 weeks, and patients with all HSV keratitis subtypes experienced an improvement in BCDVA. Table 3 summarizes the frequencies of ocular complications of the

Table 1. Socio-demographic and clinical characteristics of 72 patients with HSV keratitis

Variable	Value
Age (y), Mean ± SD	45.86 ± 16.06
Sex (Male / Female), n (%)	48 (66.7) / 24 (33.3)
Laterality (Monocular/Binocular), n (%)	70 (97.2) / 2 (2.8)
Nationality (Kuwaiti/Egyptian/Other Arab/Other non-Arab), n (%)	23 (31.9) / 16 (22.2) / 17 (23.6) / 16 (22.2)
Previous ocular history	
Ocular infection, n (%)	25 (34.7)
Ocular surgery, n (%)	5 (6.9)
Trauma, n (%)	4 (5.6)
Glaucoma medication, n (%)	2 (2.8)
Not available, n (%)	4 (5.6)
None, n (%)	32 (44.4)
Systemic disease	
Diabetes mellitus, n (%)	4 (5.6)
Cardiovascular disease, n (%)	2 (2.8)
Rheumatic disease, n (%)	5 (6.9)
Not available, n (%)	5 (6.9)
None, n (%)	56 (77.8)
Mean BCDVA at presentation (logMAR), Mean ± SD	0.57 ± 0.33
HSV keratitis subtype	
Dendritic ulcer, n (%)	22 (30.6)
Geographic ulcer, n (%)	6 (8.3)
Stromal keratitis without ulceration, n (%)	8 (11.1)
Stromal keratitis with ulceration, n (%)	9 (12.5)
Endotheliitis, n (%)	27 (37.5)

Abbreviations: HSV, herpes simplex virus; y, years; SD, standard deviation; n, number of patients; %, percentage; BCDVA, best-corrected distance visual acuity; logMAR, logarithm of the minimum angle of resolution.

Table 2. BCDVAs of the HSV keratitis subtypes at presentation and after treatment; follow-up durations

Keratitis subtype	BCDVA (logMAR)		Follow-up duration (w), Median (Q1 – Q3)
	Before treatment, Mean ± SD	After treatment, Median (Q1 – Q3)	
Dendritic ulcer	0.37 ± 0.26	0.1 (0.0 – 0.2)	4 (2.0 – 4.0)
Geographic ulcer	0.77 ± 0.28	0.3 (0.3 – 0.6)	4 (3.5 – 12.0)
Stromal keratitis without ulceration	0.54 ± 0.12	0.1 (0.1 – 0.3)	11 (7.0 – 12.0)
Stromal keratitis with ulceration	1.06 ± 0.36	0.4 (0.2 – 0.9)	12 (12.0 – 12.0)
Endotheliitis	0.52 ± 0.24	0.2 (0.1 – 0.3)	12 (8.0 – 12.0)
All included eyes with HSV keratitis	0.57 ± 0.33	0.2 (0.1 – 0.3)	10 (4.0 – 12.0)

Abbreviations: BCDVA, best-corrected distance visual acuity; HSV, herpes simplex virus; logMAR, logarithm of the minimum angle of resolution; w, weeks; SD, standard deviation; IQR, interquartile range. Note: The IQR is the difference between the first quartile (Q1, the 25th percentile) and the third quartile (Q3, the 75th percentile): IQR = Q3 – Q1.

HSV keratitis subtypes detected at the final follow-up after treatment. Corneal haze and neovascularization were detected in 54 (75.0%) and 24 (33.3%) patients, respectively (Table 3).

Figures 1 – 3 show sample slit-lamp photographs of three eyes with HSV keratitis before and after treatment.

Table 3. Frequencies of ocular complications detected at final follow-up after treatment of the HSV keratitis subtypes

Complications \ Keratitis subtype	Dendritic ulcer	Geographic ulcer	Stromal keratitis without ulceration	Stromal keratitis with ulceration	Endotheliitis	Total
Corneal haze, n (%)						
None	9 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (12.5)	18 (25.0)
Mild	11 (15.3)	4 (5.6)	7 (9.7)	4 (5.6)	16 (22.2)	42 (58.3)
Moderate	2 (2.8)	2 (2.8)	1 (1.4)	2 (2.8)	2 (2.8)	9 (12.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)	0 (0.0)	3 (4.2)
Corneal neovascularization, n (%)						
None	21 (29.2)	1 (1.4)	2 (2.8)	2 (2.8)	22 (30.6)	48 (66.7)
One quadrant	1 (1.4)	4 (5.6)	6 (8.3)	3 (4.2)	5 (6.9)	19 (26.4)
Two quadrants	0 (0.0)	1 (1.4)	0 (0.0)	2 (2.8)	0 (0.0)	3 (4.2)
≥ Three quadrants	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	0 (0.0)	2 (2.8)

Abbreviations: n, numbers; %, percentage.

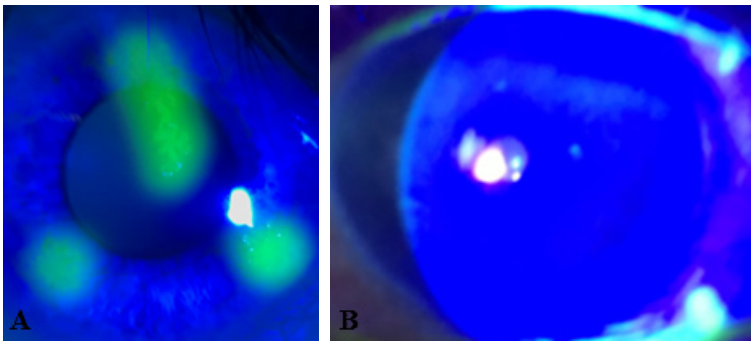

Figure 1. (A) Slit-lamp photograph at time of presentation in a patient with epithelial keratitis. Note the multiple dendritic lesions with terminal bulbs with a typical fluorescein staining appearance. (B) Lesions resolved after administration of a proper treatment regimen [21].

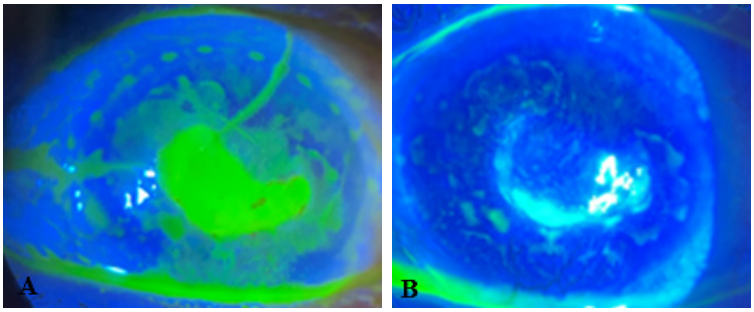

Figure 2. (A) Slit-lamp photograph with fluorescein staining in a patient with stromal keratitis with ulceration at presentation. (B) Stromal keratitis resolved after administration of a proper treatment regimen [21].

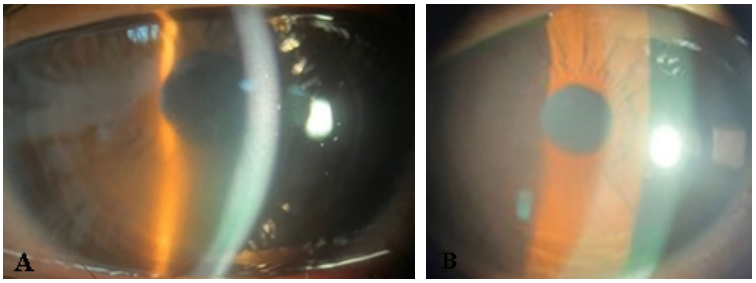

Figure 3. (A) Slit-lamp photograph of a patient with disciform endothelial keratitis at presentation, demonstrating a central area of endothelial and posterior stromal opacification with overlying stromal edema accompanied by anterior chamber cells and flare with a few fine keratic precipitates on the endothelium. (B) Endothelial keratitis resolved after administration of a proper treatment regimen [21].

DISCUSSION

The frequency of HSV keratitis in this hospital-based study was 31.7%. Most patients were men with unilateral involvement and decreased corneal sensation, and the mean age was 45.86 years at first presentation. Endotheliitis was the most common subtype, followed by dendritic epithelial ulcer. The BCDVA values differed significantly between the HSV keratitis subtypes before and after treatment. At presentation, BCDVA was significantly better in eyes with dendritic epithelial ulcers than in eyes with geographic epithelial ulcers or with HSV stromal keratitis with ulceration, better in eyes with HSV stromal keratitis without ulceration than in eyes with HSV stromal keratitis with ulceration, and better in eyes with endotheliitis than in eyes with HSV stromal keratitis with ulceration. Most eyes were treated within 1 – 2 weeks, and patients with all subtypes of HSV keratitis experienced an improvement in BCDVA. However, BCDVA in eyes with dendritic epithelial ulcers remained significantly better than that in eyes with geographic epithelial ulcers or HSV stromal keratitis with ulceration.

There are approximately 5.9 – 20.7 new cases of HSV keratitis per 100 000 individuals every year [14]. Based on the results of a 30-year retrospective study [23], in the USA alone, there are 11.8 new cases per 100 000 individuals every year. In our study, 227 patients presented with keratitis of any cause within a year, and 72 (31.7%) were diagnosed with HSV keratitis. This is a substantial number for such a small population. There have been no previous studies on the prevalence of HSV keratitis or the frequency of cases observed in the hospitals of our region.

A study by Lobo et al. [2] indicated that differences in susceptibility to HSV keratitis according to sex were unclear. Various studies have shown an increased incidence of HSV keratitis in female individuals, whereas there is an increase in disease recurrence in male individuals, possibly owing to a greater female immune response [2, 24]. Male patients also tend to have more severe infections than do female patients [2]. In our sample of patients with HSV keratitis, men outnumbered women, which contradicts the findings of the aforementioned study. However, as previously mentioned, results of the available studies vary. For instance, most studies in India have shown a higher disease incidence in male individuals [25], whereas a study in France showed similar incidences between the sexes [26].

The mean age of our patients with HSV keratitis was 45.86 years. A study by Shah et al. [14] reported a mean age of approximately 41 years, which was higher than that in similar studies conducted in India and Nepal [25, 27, 28]. Das et al. conducted a study of 8897 eyes of 8308 patients in South India, finding that the individuals most commonly affected were those in the third to fifth decades of life [25]. Studies in the USA and UK reported mean ages of 37.4 and 25 years, respectively, for the first occurrence of ocular HSV-1 [29]. However, in a global review, the age ranges in studies conducted in Europe and the USA were 37 – 54 years [10]. The mean age varies from country to country, and the higher mean age found in our study warrants investigation of the age-adjusted prevalence [30] of HSV keratitis among people within the GCC region for further comparison. In our series, 97.2% of patients had unilateral manifestations, a percentage consistent with those of global reviews [6, 10].

In a study by Shah et al. [14], most patients presented with stromal keratitis without ulceration, followed by endotheliitis [14]. Kabra et al. reported similar findings, with stromal keratitis being the most common presentation [27]. However, Labetoulle et al. reported that epithelial keratitis was the most common presentation [26]. Global estimates have reported that epithelial keratitis contributes the most to HSV keratitis incidence [10]. In contrast to most studies, endotheliitis was the most common disease entity in our study, followed by dendritic ulcers, stromal keratitis with ulceration, stromal keratitis without ulceration, and geographic ulcers. The presentations are variable and can be correlated to changes over time [3] or to different presentations depending on the global region [3].

BCDVA improved in most of our patients, and most cases were treated within the first 1 – 2 weeks. Patients with all subtypes of HSV keratitis experienced improvements in BCDVA. Corneal haze and neovascularization were detected in 54 (75.0%) and 24 (33.3%) patients, respectively, after treatment. These findings highlight the difficulties faced in treating this infectious disease. New preventive proposals, such as the development of vaccines, are worth exploring [3].

To our knowledge, this study is the first to highlight the frequency and visual outcomes of HSV keratitis in a Kuwaiti tertiary referral eye center. It provides insight, however small, into the disease in the GCC region, and the results require further verification. However, most of our patient data were derived from non-Kuwaiti patients. This included people of different backgrounds and ethnicities, making it challenging to identify the association between HSV keratitis and specific populations. The study was undertaken with a small sample of patients who presented within a 1-year time period; however, we included all cases diagnosed with HSV keratitis during this time. In addition, the sample was drawn from only one of many major hospitals in Kuwait. We have mentioned the unavailability of similar studies within the region, leaving no opportunity for comparisons. Owing to the high

and growing rates of HSV keratitis worldwide, as well as the globally inconsistent data available, it is difficult to estimate the true burden of this disease. Further multicenter population-based studies, including Kuwait and other GCC, are required to determine the prevalence and burden of this potentially blinding infectious disease in this region. Research on a larger scale is necessary to grasp the impact of HSV keratitis on the surrounding area and to combat this sight-threatening disease.

CONCLUSIONS

More than one-third of infectious keratitis cases in this hospital-based study were caused by HSV. Similar to the global trend, most of our patients had unilateral involvement with decreased corneal sensation. However, their ages at presentation were greater, men outnumbered women, and the endotheliitis subtype was the most common. Timely standard treatment interventions based on valid guidelines resulted in BCDVA improvement in all subtypes of HSV keratitis in our series, indicating the importance of early treatment. However, the BCDVA in eyes with dendritic epithelial ulcers remained substantially better than that in eyes with geographic epithelial ulcers or HSV stromal keratitis with ulceration, signifying the effect of the initial HSV keratitis subtype on visual outcomes. Further population-based studies are needed to accurately estimate disease prevalence and burden.

ETHICAL DECLARATIONS

Ethical approval: This study was approved by the Medical Ethics Committee of the Kuwait Ministry of Health. The study protocol was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.
Conflict of interest: None.

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