Herpes simplex virus (HSV) is characterized by its ability to remain latent in the nervous system. Reactivation from the ophthalmic branch of the trigeminal ganglion may lead to herpes simplex keratitis (HSK). Herpes keratitis is a common disease, with a prevalence of 150 in 100,000 inhabitants in western countries and an annual incidence ranging from 10 to 30 per 100,000 individuals. Globally, the lifetime risk of developing HSK is 1%. After the first episode, the cumulative risk of relapse is 22%, 40%, and 67% at 2, 5, and 7 years, respectively. Forty percent of patients experience 2 to 5 relapses over a lifetime, and 11% experience 6 to 15 relapses. In patients with relapsing HSK, the 3 main types of keratitis (epithelial, stromal, and endothelial) may occur in combination or successively.

Fifteen percent of all patients with HSK develop severe complications. Pain is the most significant complication in cases of acute epithelial keratitis, whereas stromal and endothelial HSK are characterized by vision loss. In the majority of cases, the vision improves as the first episode of HSK resolves. However, visual impairment occurs in up to 22% of affected eyes as the result of residual corneal scars. Over 5 years, visual acuity (VA) below 20/40 occurs in 30% of eyes with stromal HSK and 58% of eyes with endothelial HSK. Approximately 11% of patients with any history of HSK have a final VA below 20/200. Even in patients with HSK with apparently complete recovery of corneal transparency and vision using the conventional VA scales (i.e., 20/20 or logarithm of the minimum angle of resolution [logMAR] 0), some higher order aberrations, and irregular astigmatism persist, reducing the optical quality of the eye. Thus, despite an apparently complete recovery of VA, the decrease in optical quality may lead to symptoms of decreased visual function.

Other potential complications of HSK include persistent loss of corneal sensitivity, impaired epithelial healing, and chronic inflammation even during the quiescent phase of the disease. Moreover, although recurrent episodes of HSK affect the same eye in more than 90% of patients, both eyes may develop dry eye disease (DED), proportional to the severity of unilateral HSK, because of an impaired lacrimal system. The latter arises from damage to the neuronal terminations in the herpetic cornea and degeneration of the corresponding trigeminal nerve fibers.
The observations on the quality of vision and the pain and discomfort caused by secondary bilateral DED indicate that quality of life (QoL) may be impaired in patients with HSK. This topic has not been specifically assessed in the literature despite the relatively high frequency of HSK. Hoeksema and Los reported a reduction of QoL in patients with anterior herpetic uveitis. However, their conclusions cannot be extrapolated to patients with HSK because of the differing levels of pain and visual impairment between keratitis and uveitis. Li et al. reported reduced QoL in patients with various types of infectious keratitis, including HSK; however, separate analyses of HSK were not reported. In this study, we evaluated the QoL in patients with a history of multiple episodes of unilateral HSK using 3 validated ophthalmic QoL questionnaires.

Methods

Patients and Enrollment Criteria

This prospective, noninterventional, case-controlled study evaluated the QoL of patients with unilateral and recurrent HSK (HSK group). All patients referred to the Department of Ophthalmology at Bicêtre Hospital, Le Kremlin-Bicêtre, France, between December 2013 and March 2014 with a history of unilateral and recurrent HSK were prospectively considered for inclusion. The diagnosis of presumed HSK was based on the combination of (1) a history of recurrent episodes of unilateral keratitis; (2) the presence of corneal opacities highly suggestive of HSK (or by default, a history of dendritic or geographic epithelial defect); (3) the efficacy of antitherpetic drugs (oral valaciclovir, oral or topical acyclovir, topical ganciclovir or trifluridine) for the treatment of previous episodes; and (4) no history of herpes zoster (regardless of location).

Patients were included in the study if they were older than 18 years of age, were fluent in French, and had a history of HSK with at least 2 episodes during the previous 4 years. Herpes keratitis had to be quiescent at enrollment and during the previous 3 months, and best-corrected VA of the unaffected fellow eye had to be within 0 and 0.3 logMAR. The exclusion criteria were any inflammatory event consistent with a herpetic episode in the fellow eye, the occurrence of any viral or ocular inflammatory episode in the affected eye during the previous 3 months, a history of any disease or pathology other than a refractive error (myopia < −4 diopters [D], hyperopia < +4 D, astigmatism < +3 D), best-corrected VA within normal limits (0–0.1 logMAR) in both eyes, no history of contact lens use, incomplete lid closure or abnormal lid position, obstruction of nasolacrimal system, punctal plugs (or punctal cautery), ocular allergy, severe lid abnormalities including seborrheic dermatitis or rosacea (with meibomian gland disease), the use of any systemic medication that could interfere with tear secretion (e.g., β-blockers or medications with antimuscarinic effects). A comprehensive clinical examination was performed on all patients in the control group to confirm the absence of subjective or objective signs of any ocular surface disease.

Questionnaires

The 3 questionnaires that were used for both patients and controls included the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), Glaucoma Quality of Life 17 (Glau-Qol17) questionnaire, and Ocular Surface Disease Quality of Life (OSD-QoL) questionnaire. The NEI VFQ-25 was validated as a short version of the NEI VFQ. The purpose of this self-administered questionnaire is to assess health-related QoL in any eye disease that causes decreased vision. It contains 25 items exploring 12 dimensions. We used this questionnaire because it was previously used in a large number of QoL studies for chronic and acute ocular diseases of various causes (e.g., age-related macular degeneration, diabetic retinopathy, cataract, glaucoma, infectious and inflammatory eye diseases), and the French version was validated in 2004.

The French version of the Glau-Qol17 questionnaire was validated in 2003. It contains 17 items that evaluate 7 domains (anxiety, self-image, mental state, daily living, driving, limitation, and management). It is the short form of the Glau-Qol36 questionnaire (36 items), initially developed to explore the QoL in patients with glaucoma.

The OSD-QoL questionnaire was developed by a French group to assess QoL in ocular surface diseases. It contains 28 items covering 7 areas: daily activities, disability and discomfort related to work (handicap), makeup, disease recognition (acknowledgement), acceptance of illness, fear of the future, and emotional well-being. This questionnaire was included to specifically address the consequence of chronic and bilateral DED caused by the recurrent episodes of HSK.

The results of the questionnaires were compared between groups. In the HSK group, the results of the questionnaires were analyzed on the basis of the 5 criteria in the medical history: the duration of the disease, relapse frequency, patient age, and VA in the affected eye and in the unaffected eye.

Ethics Statements

This study adhered to the tenets of the Declaration of Helsinki. Institutional Review Board (IRB)/Ethics Committee approval was obtained from the Ethics Committee of the French Society of Ophthalmology (IRB 00008855 Société Française d’Ophtalmologie IRB#1). All subjects (patients and controls) provided written informed consent.

Statistical Analysis

Strict patient anonymity was maintained during data collection. Statistical analysis was performed with STATA (StataCorp LP, College Station, TX) and GraphPad Prism 6 (GraphPad Software, Inc, La Jolla, CA). Visual acuity was initially measured in decimal notation and then converted to logMAR for statistical analysis. Continuous variables were analyzed with the Student t test. The nonparametric Spearman test was used to evaluate correlations. Statistical significance was indicated by P < 0.05 (2-tailed).

Results

Clinical Characteristics of Patients and Controls

There were 33 patients in the HSK group and 66 patients in the control group. Table 1 presents patient demographics and clinical
Acuity. In the affected eye of patients with HSK, VA was 0.63 logMAR in the affected eye. A prophylactic antiviral treatment at time of inclusion was negatively correlated with the dimension “ocular pain” (rho = 0.414, P = 0.02), which indicates that QoL related to daily activities is negatively affected by the duration of the disease.

Impact of the Medical History and Severity of Herpetic Ocular Disease on Quality of Life

The results of Spearman’s test for potential correlations are plotted in Figure 2.

Duration of Disease. The only statistically significant correlation between the duration of the disease and the results in the 3 questionnaires (Fig 2A) was with the dimension “limitation” in the Glau-QoL17 questionnaire (rho = 0.414, P = 0.02), which indicates that QoL related to daily activities is negatively affected by the duration of the disease.

Frequency of Relapses. The frequency of relapses (Fig 2B) was negatively correlated with the dimension “ocular pain” of characteristics. The majority of patients with HSK (62.86%) presented with stromal keratitis as the predominant type (>50%) of recurrences, 42% had a history of herpetic disease for more than 10 years, 45% experienced more than 1 episode of HSK yearly before the study period, and 82% were receiving prophylactic antiviral therapy. In patients with HSK, VA was decreased in 58% of the affected eyes (mean VA in the affected eye was 0.63±0.88 logMAR and 0.03±0.11 logMAR in the unaffected eye). The mean VA in the control group was 0.006±0.02 logMAR (both eyes).

Comparison of Questionnaires between Groups

National Eye Institute Visual Functioning Questionnaire. The results of the NEI VFQ-25 are presented in Table 2. There was a significant difference between groups for the total score and for each of the 12 dimensions (P < 0.05 for all comparisons) (Table 2). For some aspects of QoL, the mean scores were strikingly lower in the HSK group compared with the control group, for example, for “ocular pain,” “mental health,” “general vision,” and “role difficulties.” Almost all scores in the control group were >80, denoting good QoL. The opposite was observed for the HSK group, in which only “color vision” and “social function” scored >80. These 2 dimensions were statistically significantly lower in the HSK group compared with the control group (P < 0.05, both comparisons).

Glaucoma Quality of Life Questionnaire. The results of the Glau-QoL17 questionnaire are presented in Table 3. All mean scores were >80 in the control group, and <80 in the HSK group. The difference was statistically significant between groups for the total score and for 6 of the 7 dimensions explored in this questionnaire (P < 0.05 for all comparisons, except for the dimension “limitation”). The maximal difference was observed for the dimensions “mental state” (57.9 for the HSK group vs. 93.9 for the control group), “anxiety,” “driving,” and “management.”

Ocular Surface Disease-Quality-of-Life Questionnaire. A significant difference was observed between groups for the total score and for each of the 7 dimensions (Table 4). The HSK group had lower mean scores that the control group for “fear” and “makeup.” All mean scores except “acknowledgment” were >80 in the control group, whereas all mean scores except “acceptance” were <80 in the HSK group. Results of the 3 questionnaires for both groups are plotted in Figure 1.

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the NEI VFQ-25 (rho = -0.4, P = 0.02), whereas the dimension “acknowledgement” in the OSD-QoL questionnaire was positively correlated with the frequency of episodes (rho = 0.4, P = 0.04). There was a greater impact of pain (and memory of pain from previous episodes) on the QoL in patients with more frequent recurrences.

Age. Age was negatively correlated with “general health” (rho = -0.4, P = 0.02) and “color vision” (rho = -0.4, P = 0.036) on the NEI VFQ-25 (Fig 2C), which also may be related to comorbidities, especially lens opacities.

Visual Acuity. Visual acuity in the affected eye (Fig 2D) was negatively correlated with several dimensions of the NEI VFQ-25: “general vision” (rho = -0.4, P = 0.009), “distance activities” (rho = -0.5, P = 0.002), “social function” (rho = -0.5, P = 0.003), “dependency” (rho = -0.4, P = 0.039) and “peripheral vision” (rho = -0.3, P = 0.04) (Fig 2D). For the Glau-QoL17 questionnaire, an inverse correlation was also found for “self-image” (rho = -0.4, P = 0.02), “daily living” (rho = -0.4, P = 0.03), “driving” (rho = -0.4, P = 0.009), and the total score (rho = -0.5, P = 0.008). In contrast, no significant correlation was observed between VA in the affected eye in the HSK group and the results of the OSD-QoL questionnaire.

The VA in the unaffected eye (Fig 2E) was inversely correlated with “self-image” (rho = -0.4, P = 0.03) and “driving” (rho = -0.4, P = 0.009) in the Glau-QoL17 questionnaire. Likewise, the VA in the unaffected eye was positively correlated with “makeup” results in the OSD-QoL questionnaires (rho = 0.3, P < 0.0001).

### Discussion

The outcomes of the current study indicate that QoL is altered in patients with a history of recurrent unilateral HSK compared with a control population of unaffected patients. This was observed in the total scores for each of the 3 questionnaires used in this study and in almost all the dimensions tested. Among the 5 criteria evaluated for correlations with QoL results, VA in the affected eye had the greatest impact on reducing the QoL of patients with HSK.

### Recurrent Herpes Simplex Keratitis Induces Significant and Persistent Loss of Quality of Life

In the HSK group, the lowest scores on the 3 questionnaires were those of QoL related to mental health and ocular pain. Because patients were included during a quiescent phase of the disease, this outcome suggests that pain occurring during acute HSK episodes has long-term effects on the QoL and can result in a persistent psychologic impact on mental health. The subanalysis outcomes of QoL, based on the frequency of relapses, concur with this observation: Ocular pain scores were even worse in patients with more than 1 recurrence per year compared with the others. Previous studies have documented that recurrent episodes impair corneal innervation, resulting in persistent corneal hypesthesis.16,26 Rather than persistent pain between acute episodes, the scores related to ocular pain score thus could be explained by the memory of the painful experience or the fear of an impending painful relapse. Another explanation is the effect of recurrent HSK on ocular surface quality. Unilateral recurrent HSK induces bilateral DED over time,14 and, regardless of the initiating mechanism, DED induces a significant reduction in the QoL of patients.25

We observed that the results in all vision-related dimensions of the QoL questionnaires (daily activities, social behavior, sociability, and dependency) were significantly correlated to the VA in the affected eye. These outcomes concur with recent publications on the general relationship between visual function and social behavior.27,28 Ocular herpetic keratitis is considered the primary cause of acquired blindness of infectious origin in developed countries10 because of its prevalence and the substantial decrease in vision (<20/200) that eventually occurs in up to 10% of patients.22 Taken together, our results and those of previous studies emphasize the impact of unilateral decreased VA caused by HSK on the global QoL. A similar observation was recently published by Vashist et al30 for other types of unilateral corneal diseases.
Greater Decrease in Quality of Life Due to Herpes Simplex Keratitis Compared with Other Types of Infections of the Anterior Segment

Before this study, QoL in patients with herpetic eye disease had been tested only within the spectrum of anterior uveitis. A mean NEI VFQ-25 total score of 88.1 was reported, whereas the mean result was 70.5 in our series (Table 5). Similar differences between our study and the study by Hoeksema and Los are present for all the dimensions of the questionnaire. However, comparison between studies may not be entirely accurate. These differences could be cultural (e.g., lower level of tolerance to ocular disease in some countries compared with others), but they more likely reflect higher perception of pain when the cornea is affected (in keratitis vs. uveitis) and the higher prevalence of decreased vision due to corneal scars. By evaluating other types of infectious causes of keratitis, Li et al reported a mean score of 58.1 for the NEI VFQ-25 and even lower scores with short-term ocular infections (Table 5). The authors attributed this result to the sudden onset of the infection, causing a shock in the patient’s life. Perhaps a longer evolution of the disease may help the patient get accustomed to the idea of the eventual loss of vision. In the current study, we found no clear correlation between duration of disease (>10 years or <10 years) and QoL, regardless of the questionnaire (with the exception of the dimension “limitation” in the Glau-QoL17 questionnaire). This is likely due to the intermittent nature of HSK, with long quiescent periods between the acute episodes and the decrease in vision that manifests surreptitiously over several years. However, we found a correlation between the frequency of relapses and the dimension “ocular pain” on the NEI VFQ-25. This outcome concurs with the findings of Li et al and indicates that frequent relapses result in lower QoL due to the painful episodes (or the memory of pain). Likewise, there was a correlation between the frequency of relapses and the dimension “acknowledgement” on the OSD-QoL questionnaire. This outcome suggests that relatives of patients had greater awareness and knowledge of the decreased QoL in patients with more frequent relapses of HSK. Unfortunately, Li et al did not assess the differences in QoL between infectious causes; thus, comparison with our results should be interpreted with caution.

Greater Decrease in Quality of Life Due to Unilateral Herpes Simplex Keratitis Compared with Noninfectious Binocular Diseases of the Ocular Surface

In this study, the outcomes of the NEI VFQ-25 in the unilateral HSK patients were worse than those previously
Figure 2. Radar graphs plotting the correlation analyses (Spearman’s test) among 5 clinical variables of the herpetic disease and scores of quality of life (QoL) questionnaires (NEI VFQ-25, OSD-QoL, and Glau-QoL17) in patients with unilateral HSK. Violet and blue line represents the correlation between a history of herpetic disease for >10 years (A) and >1 herpetic recurrence per year (B), respectively, and the scores in the 3 questionnaires. Orange, red, and green lines present the relation among age (C), visual acuity (VA) in the affected eye (D), and VA in the unaffected eye (E), respectively, and the scores in the 3 questionnaires. Axis legend: A point at the center of the circle means a significant proportional correlation between the clinical variable tested and the result of the questionnaire (positive rho with \( P < 0.05 \)), whereas a point on the outer circle means an inversely proportional correlation (negative rho with \( P < 0.05 \)). A point on the intermediate circle means no significant correlation (\( P > 0.05 \)). Glau = Glaucoma Quality of Life 17 questionnaire; NEI = National Eye Institute Visual Functioning Questionnaire-25; OSD = Ocular Surface Disease Quality of Life questionnaire.
reported for chronic and bilateral ocular surface diseases such as conjunctivochalasis,30 Sjögren-related DED,31 and even ocular graft-versus-host disease (GVHD),32 which is considered one of the most severe ocular surface disease. A component of the reduced QoL in patients with HSK may be related to the secondary bilateral DED,32 and DED has a negative influence on the quality of vision per se.44 Compared with Sjögren or GVHD–related DED, the lower results observed in our series suggest that factors other than DED dramatically reduce QoL in patients with HSK. The QoL related to “ocular pain” in the HSK group in the current study (53.3±29.5) was lower than previously described in patients with Sjögren’s31 and GHVD32 (66.7±22.2 and 60.8±24, respectively). Likewise, the QoL related to “general vision” was lower in our series than for patients with Sjögren’s31 and GHVD32 (65.0±18.03 vs. 78.6±12.8 and 69.1±16, respectively). Both the risk of vision loss5 and the reduced visual quality despite an apparently complete recovery of corneal transparency12 may explain this finding. With time, recurrent episodes of pain or loss of vision likely induce anxiety in patients with HSK, as indicated by the score related to the “mental health” dimension (NEI VFQ-25), which was lower in patients with HSK (55.5±27.65) than in those with Sjögren’s31 and GHVD32 (83.1±17.5 and 67.2±26, respectively).

The OSD-QoL questionnaire is focused on QoL specifically related to ocular surface abnormalities, providing interesting results that can be compared with the study by Baudouin et al12 of various ocular surface diseases (mostly DED). Some of the outcomes for the HSK group in our study were better than for patients with pure DED, especially for “acceptance” (84.1 vs. 72.1, respectively), “handicap” (74.3 vs. 64.9, respectively), and “acknowledgment” (52.93 vs. 39.6, respectively) (Fig 3). In the HSK group, patients’ acceptance of the disease and their self-image in relation to their relatives appears higher than for other causes of DED, which is likely due to the obvious nature of HSK disease during acute episodes (e.g., sudden onset, pain, redness) in contrast to the apparently

<table>
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<tr>
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AMD = age-related macular degeneration; HSK = herpes simplex keratitis; SD = standard deviation.
Average of the total score and standard deviation are indicated, because they were the only common data between studies.
been associated with lower NEI VFQ-25 results than those of the HSK group in the current study. 

Although comparison between our series of patients with HSK and previous studies is challenging, the same questionnaire (NEI VFQ-25) has been used in all investigations.

**Study Limitations**

A drawback of the present study was the absence of a questionnaire specifically designed for patients with HSK, which is currently unavailable. Thus, we elected to evaluate QoL with well-established vision-related survey instruments, even if none of them perfectly fit all the problems encountered by those with HSK.

The NEI VFQ-25 is mainly focused on the relation between QoL and vision disabilities. Even if patients included in our study had normal vision in the unaffected eye and a minimal 3-month period free of any herpetic episode, the NEI VFQ-25 results clearly show the persistent loss of QoL related with loss of vision in patients with HSK. Because 42% of the affected eyes had recovered normal vision, it is likely that vision-related QoL is worse during an active episode of HSK, an issue that was out of the scope of this study.

The use of the Glau-QoL17 questionnaire was based on the observation that glaucoma and HSK share a poor long-term prognosis despite an apparently benign onset over the first few years. The outcomes provided important information about psychologic consequences of HSK, including anxiety of losing sight in the distant future and lowering of self-image.

The OSD-QoL questionnaire initially was built for chronic ocular surface conditions, such as common causes of DED (e.g., Sjögren syndrome), instead of relapsing conditions. However, some ocular surface disorders persist in HSK, and outcomes on fear, acceptance, and acknowledgment demonstrated the stressful nature of HSK for the patient over the long-term despite temporary relapses.

Another drawback of this study involves the type of patients enrolled because our department is a tertiary care center for HSK. Thus, most of patients were referred for a history of moderate to severe HSK. This could have biased our results toward a greater impact on QoL. However, the specific population of patients with recurrent and severe HSK accounts for approximately 40% of cases and represents a real challenge for ophthalmologists who have to deal with both the severity of the disease and patient anxiety.

In summary, this study shows that even during the quiescent phase of the disease, patients with relapsing and unilateral HSK present with a severe and persistent impairment of QoL, with a level that is similar to most sight-threatening diseases. The vision-related QoL is mainly correlated with VA in the affected eye and with the number of relapses per year. Accounting for these aspects could be helpful for physicians to further understand the symptoms and psychologic status of herpetic patients, even when the ocular disease is not active. The results obtained in the present study will be useful in developing a new universal metric that can reveal the impact of HSK during quiescent periods and for comparison with other sight-threatening conditions.


Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

- D = diopeters
- DED = dry eye disease
- Glau-QoL17 = Glaucoma Quality of Life 17
- HSK = herpes simplex keratitis
- HSV = herpes simplex virus
- IRB = Institutional Review Board
- logMAR = logarithm of the minimum angle of resolution
- NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25
- OSD-QoL = Ocular Surface Disease Quality of Life
- QoL = quality of life
- VA = visual acuity

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Pictures & Perspectives

“Twin Peaks” Papilledema

A 10-year-old girl with a history of chiasmal glioma presented with headaches, dysarthria, disorientation, and incontinence. Visual acuity was 20/25 in the right eye. The left eye demonstrated an afferent pupillary defect, vertical nystagmus, and a visual acuity of 20/50. Retinal examination showed superior and inferior optic disc edema (right eye worse than left eye) and retinal nerve fiber (RNFL) layer loss nasally and temporally in both eyes (Fig 1, top). Optical coherence tomography showed “twin peaks” corresponding to the distended superior and inferior RNFL in both eyes (Fig 1, bottom). Bilateral “twin peaks” papilledema localizes the intracranial lesion to the suprasellar region with selective injury to the decussating chiasmal fibers.

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