AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Persistent Impairment of Quality of Life in Patients with Herpes Simplex Keratitis

Clotilde Reynaud, MD,[1] *Antoine Rousseau, MD,*[1,2] *Godefroy Kaswin, MD,*[1] *Mohamed M'garrech, MD,*[1] *Emmanuel Barreau, MD,*[1] *Marc Labetoulle, MD, PhD*[1,2]

Purpose: To evaluate the quality of life (QoL) in patients with quiescent herpes simplex keratitis compared with control patients without ocular herpes.

Design: Prospective, case-control study.

Participants: Thirty-three patients with a unilateral and relapsing herpes simplex keratitis (HSK group) that was quiescent during evaluation (no acute episode in the past 3 months) and 66 patients with no history of HSK (control group). Both groups were age and gender matched.

Methods: Three previously validated QoL questionnaires were used in this study: 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. Each questionnaire covered various aspects of the disease.

Main Outcome Measures: The outcomes of the 3 questionnaires were compared between groups. For the HSK group, the results were correlated to the clinical findings and the history of herpetic disease.

Results: The mean total questionnaire scores of the 3 QoL questionnaires were significantly lower in the HSK group compared with controls (NEI VFQ-25: 70.5±3.8 vs. 91.1±0.8, $P < 0.0001$; Glau-QoL17: 68.2±3.1 vs. 87.9±1.0, $P < 0.0001$; and OSD-QoL: 65.4±2.9 vs. 93.1±0.6, $P < 0.0001$, respectively). In the HSK group, the level of visual acuity (VA) in the affected eye had the greatest impact on QoL, inducing lower QoL results related to "general vision," "distance activities," "dependency," "peripheral vision," "self-image," "daily living," and "driving" dimensions. Decreased VA in the unaffected eye also negatively affected "self-image" and "driving" results. Patients with frequent HSK relapses had lower QoL related to "ocular pain" and "acknowledgement."

Conclusions: Even during a quiescent phase of the disease, unilateral and relapsing HSK significantly impairs the QoL of patients to a similar level as most sight-threatening diseases. The decrease of VA has the greatest overall effect, but other factors also significantly affect QoL, such as the frequency of relapses. *Ophthalmology 2016;■:1–10 © 2016 by the American Academy of Ophthalmology*

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).[1,2] Herpes keratitis is a common disease, with a prevalence of 150 in 100 000 inhabitants in western countries[3] and an annual incidence ranging from 10 to 30 per 100 000 individuals.[3–5] 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.[6,7] Forty percent of patients experience 2 to 5 relapses over a lifetime, and 11% experience 6 to 15 relapses.[8] 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.[9] 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.[10] Over 5 years, visual acuity (VA) below 20/40 occurs in 30% of eyes with stromal HSK and 58% of eyes with endothelial HSK.[11] Approximately 11% of patients with any history of HSK have a final VA below 20/200.[5] 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.[12] Thus, despite an apparently complete recovery of VA, the decrease in optical quality may lead to patient 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.[1,13] Moreover, although recurrent episodes of HSK affect the same eye in more than 90% of patients,[7,10] both eyes may develop dry eye disease (DED), proportional to the severity of unilateral HSK,[14] because of an impaired lacrimal system.[15] The latter arises from damage to the neuronal terminations in the herpetic cornea[16] and degeneration of the corresponding trigeminal nerve fibers.[17]

http://dx.doi.org/10.1016/j.ophtha.2016.10.001
ISSN 0161-6420/16

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[18] reported a reduction of QoL in patients with anterior herpetic uveitis. However, their[18] 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[19] 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 antiherpetic 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 corneal or intraocular surgery in the year preceding the study, 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 history (past or ongoing) of glaucoma or glaucoma suspect, and the inability to obtain a reliable informed consent from the patient.

Controls

A control group was included of healthy individuals referred for routine ophthalmologic examination during the study period. The control group was matched for gender and age (±3 years) with the HSK group. Inclusion criteria for the control group were an age of at least 18 years, fluent in French, no history of any ophthalmic 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 wear, and no history of systemic medications 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.[20,21] 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.[22]

The French version of the Glau-QoL17 questionnaire was validated in 2003.[23] 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.[24]

The OSD-QoL questionnaire was developed by a French group to assess QoL in ocular surface diseases.[25] 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.[14]

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