Optical aberrations in patients with recurrent herpes simplex keratitis and apparently normal vision

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ABSTRACT

Aims To analyse high-order aberrations (HOA), modulation transfer function (MTF) and Strehl ratio in patients with a history of herpes simplex keratitis (HSK) and apparently normal vision.

Methods Fifteen patients with a history of recurrent unilateral HSK and normal Snellen visual acuity (0 logMAR) were enrolled. Eyes with HSK (HSK group) were statistically compared with normal fellow eyes (Control group). HOA, MTF and Strehl ratio were measured using the OPD-SCAN II (Nidek Co, Gamagori, Japan) aberrometer. Measures were performed at least 3 months after the last episode of herpes. Statistical significance was indicated by $p<0.05$.

Results Despite apparently normal vision in both eyes (as assessed by routine visual acuity charts), significantly higher total HOA, trefoil and tetrafoil were present in the HSK group compared with the Control group. The MTF and strehl ratio were lower in the HSK group compared with the Control group. In the HSK group, eyes with corneal opacities tended to present with greater optical aberrations than eyes with a clear cornea.

Conclusions Using patients as their own controls, the outcomes of this study indicate that eyes with recurrent HSK with no apparent decrease in visual acuity (0 logMAR) have significantly greater optical aberrations than eyes with no past history of herpetic disease. This outcome may explain some visual complaints of HSK patients, such as a decrease in contrast quality or reduced colour perception, compared with the unaffected contralateral eye despite apparently normal vision in both eyes.

INTRODUCTION

Ocular herpes simplex virus (HSV) keratitis is the leading cause of infectious visual loss in industrialised countries. The estimated prevalence is 150 in 100 000,[1] and the incidence ranges from 10 to 30 per 100 000 individuals.[2 3] Herpes simplex keratitis (HSK) is characterised by a high risk of recurrence that increases over time.[4] Epithelial infections (dendritic or geographic) account for 60%, while stromal keratitis and endothelial keratitis represent approximately 30% and 10%, respectively, of all HSK cases.[2] The prognosis is poor in these cases due to alteration of the stroma by viral replication, immune phenomena, and in some cases, neurotrophic damage or endothelial decompensation.[2] Hence, recurrent HSK induces a loss of vision, and approximately 11% of patients have a final visual acuity below 20/200.[3]

Despite several episodes of HSK, some patients may maintain apparently normal vision when tested with routine visual acuity charts, such as Snellen, or early treatment of diabetic retinopathy study charts. However, these patients frequently describe a difference in vision between the affected eye, compared with the unaffected eye. Wavefront analysis is helpful in investigating these complaints.

Aberrometry or wavefront analysis is used to study the objective visual quality of the eye. Aberrometry characterises the optical properties of the eye beyond simple cylindrical and spherical components and quantifies 'irregular astigmatism' into various higher-order aberrations (HOA).[5] Ocular aberrations affect retinal image quality.[6] The wavefront of an optical system is represented by mathematical decomposition into Zernike polynomials. These polynomials represent a series of elementary deformities corresponding to predefined optical aberrations classified according to radial and angular degree. Each polynomial can be weighted by a root mean square (RMS) coefficient, correlated with the deviation of the wavefront from its ideal position. The higher the value of a coefficient, the greater the role of the aberration in the entire wavefront profile. The 0–2nd order Zernike terms represent lower-order aberrations of the eye, with 2nd-order terms (ie, defocus and astigmatism) making the greatest contribution to the overall wavefront aberration of the eye. Second-order aberrations can be corrected by glasses, contact lenses or refractive surgery. Third-order and higher-order terms represent HOA. Third-order and fourth-order terms are the most prevalent HOA in the human eye. Third-order aberrations include coma and trefoil, corresponding to a defect of alignment of the elements of the optical system (shift). Fourth-order aberrations include spherical aberration, secondary astigmatism and tetrafoil, which indicate a phase shift of the peripheral aspect of the wavefront. The magnitude of aberrations increases with pupil dilation leading to a decrease in visual performance due to a degradation of optical quality of the retinal image.[7]

Other metrics that predict retinal image quality, include the modulation transfer function (MTF) which measures the attenuation of the image contrast; the point spread function (PSF), which corresponds to the distortion of a point of light on the retina and the Strehl ratio, which compares the patient's PSF with the PSF of a theoretically perfect eye.[8]

While recurrent herpetic keratitis induces corneal clouding in many patients that leads to decreased vision, others may develop translucent scars that are not severe enough to reduce visual acuity with routine testing (eg, Snellen chart). Such corneal imperfections can potentially result in optical aberrations, as any scarring will lead to scatter and irregular

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astigmatism due to wavefront abnormalities. In this study, we evaluated the distribution of higher-order aberrations in patients with recurrent unilateral (HSK) with apparently normal visual acuity of the affected eye on routine visual acuity charts.

PATIENTS AND METHODS

All patients referred to our department between February 2009 and September 2010 with a history of unilateral and recurrent keratitis presumably due to HSV, and with at least one stromal episode, were considered for inclusion in this study. Patients were included in the study if they had not presented with any acute signs of ocular inflammation for at least 3 months prior to the study and on the day of vision testing. To be eligible for the study, the best corrected visual acuity (BCVA) had to be 0 logMAR (20/22 or 20/20) in both the affected and unaffected eye, using the full-contrast Snellen chart. Patients with any eye disease potentially inducing asymmetric optical aberrations (eg, corneal infection other than herpes) or a history of ocular surgery were ineligible for this study.

The clinical diagnosis of keratitis was based on clinical notes and slit lamp examination (epithelial or stromal abnormalities typical of HSV infection). The herpetic origin of keratitis was considered in cases with a history of multiple relapses of either keratitis or keratouvetis with at least one stromal recurrence, efficacy of antiherpetic drugs (oral valacyclovir, or oral or topical acyclovir, or topical gancyclovir or trifluridine), and in the absence of a history of herpes zoster (at any site).

This study adhered to the tenets of the Declaration of Helsinki. All patients underwent a thorough informed consent procedure including an explanation of the nature of the study.

Optical aberrations were evaluated with the OPD-SCAN II aberrometer (Nidek Co, Gamagori, Japan), based on the principle of dynamic skiascopy (infrared slit refractometry) and double-pass aberrometry.

Mean RMS of total aberrations, HOA, coma, trefoil, tetrafoil, spherical aberration, MTF and the Strehl ratio were compared between the affected and unaffected fellow eyes. Mirror image symmetry (enantiomorphism) is a known property of higher-order wavefront aberrations (vertical symmetry about the median vertical axis of the face), hence, each patient served as his/her own control, and the eyes affected by HSK ('HSK group') were compared with the fellow non-affected eye ('Control group'). In the HSK group, some eyes presented with peripheral opacities (no opacities within the central 5 mm of the cornea) on slit-lamp examination (BQ900, Haag–Streit), which were not visually significant, as all subjects had 0 logMAR BCVA in both eyes. The higher-order aberrations of the HSV group with opacities were compared with eyes in the HSV group free of any corneal clouding, that is, with HSV-affected eyes and a clear cornea. All the aberrations were reported for a 6 mm pupil diameter to the 6th radial order.

Comparisons between the control group and the HSK group were performed with the Friedman non-parametric test for paired data. Comparisons in the HSK group between the 'clear cornea' group and the 'corneal opacities' group were performed with the Kruskal–Wallis non-parametric test. Statistical significance was defined as $p<0.05$ (two-tailed). A clear cornea was defined as a cornea that was as transparent as the unaffected cornea of the fellow eye on slit lamp examination (no opacity, irrespective of slit orientation).

RESULTS

Fifteen patients (seven men and eight women, mean age 41.40 ±19.9 years) with normal vision in both eyes despite a past history of at least one outbreak of stromal keratitis were enrolled in this prospective study. Due to inclusion criteria, all patients had a history of multiple episodes of unilateral and recurrent herpetic keratitis. The initial clinical feature of their herpetic disease was epithelial dendritic or geographic keratitis in five patients, pure stromal episodes in six patients and kerato-uveitis in four cases.

For seven patients, the affected cornea appeared as clear as the unaffected cornea of the fellow eye on slit lamp examination. Eight patients had some corneal opacities in the affected

Table 1 Clinical characteristics of 15 patients included in the study

	Age	Gender	Initial features	Affected eye	VA OD (logMAR)	VA OG (logMar))	Corneal opacities affected eye	Onset	Medical history	Number of recurrences/ previous year
1	46	Female	Keratouveitis	Left	0	0		2006		2
2	61	F	Epithelial	Left	0	0	(+)	1996	Hypothyroidism	0
3	44	F	Stromal	Left	0	0	(+)	1980	Hypothyroidism	4
4	48	Male	Epithelial	Right	0	0		2001	Diabetes mellitus AIDS	
5	27	F	Stromal	Left	0	0		2007		1
6	50	F	Keratouveitis	Right	0	0	(+)	1996	Genital herpes AIDS	2
7	37	M	Stromal	Right	0,1	0		1988		1
8	39	F	Keratouveitis	Left	0	0		2004	Labial herpes Psoriasis HLAB27	3
9	41	F	Epithelial	Left	0	0		2008		2
10	12	M	Epithelial	Left	0	0	(+)	2007	Labial herpes	1
11	66	F	Stromal	Right	0	0	(+)	2000		2
12	73	M	Keratouveitis	Left	0	0	(+)	1996	Diabetes mellitus	0
13	58	M	Epithelial	Left	0	0	(+)	1983	Glaucoma	0
14	12	M	Stromal	Left	0	0	(+)	2009		2
15	7	M	Stromal	Right	0	0		2009		2

All patients had a history of recurrent herpes simplex keratitis in one eye and apparently normal vision (0 logMar) in both eyes.

Table 2 Mean root mean square of aberrations (total, higher-order, coma, trefoil, tetrafoil and spherical aberrations), Modulation Transfer Function (MTF) (area under the curve) and Strehl ratio in eyes with herpes simplex keratitis (HSK) (affected eyes) and the unaffected fellow eyes of 15 patients

	Control group n=15		HSK group n=15		Affected eye/ unaffected eye difference (absolute values)	p Value
	Mean (μm)	SE	Mean (μm)	SE		
Total	1.336	±0.307	2.452	±0.495	1.116	0.083
HO	0.476	±0.122	1.045	±0.302	0.569	0.004
Coma	0.245	±0.056	0.429	±0.127	0.195	0.564
Trefoil	0.222	±0.058	0.512	±0.109	0.925	0.004
Tetrafoil	0.112	±0.052	0.296	±0.108	0.184	0.021
Spherical aberration	0.173	±0.050	0.411	±0.212	0.238	0.248
MTF	0.696	±0.064	0.450	±0.048	0.246	0.020
Strehl ratio	0.61	±0.013	0.52	±0.03	0.09	0.020

Table 3 Root mean square coefficients for aberrations (total, higher-order, coma, trefoil, tetrafoil and spherical aberrations), Modulation Transfer Function (MTF) (area under the curve) and Strehl ratio in the clear cornea group (no corneal opacities) and in the corneal opacities group of 15 eyes with herpes simplex keratitis

	No corneal opacities n=7		Corneal opacities n=8		p Value
	Mean (μm)	SE	Mean (μm)	SE	
Total	2.132	±0.457	2.651	±0.753	0.655
HO	0.831	±0.176	1.271	±0.490	0.655
Coma	0.259	±0.096	0,579	±0.184	0.055
Trefoil	0.551	±0.133	0.449	±0.139	0.482
Tetrafoil	0.266	±0.140	0.447	±0.147	0.306
Spherical aberration	0.229	±0.080	0.525	±0.360	0.655
MTF	0.507	±0.043	0.437	±0.080	0.338
Strehl ratio	0.89	±0.065	0.22	±0.08	0.179

eye, which were located outside the optical axis in all cases (table 1).

There were no significant differences between the HSK group and the control group in the mean RMS of total optical aberrations (2.452 μm and 1.336 μm, respectively, p=0.083), coma (0.429 μm and 0.245 μm, respectively, p=0.564) and spherical aberration (0.411 μm and 0.173 μm, respectively, p=0.248). There were statistically significant differences between the HSK group and the control group in the mean RMS for total HOA (1.045 μm and 0.476 μm, respectively, p=0.004), trefoil (0.512 μm and 0.222 μm, respectively, p=0.004) and tetrafoil (0.296 μm and 0.112 μm, respectively, p=0.021) (table 2, figure 1).

The MTF was 0.450±0.048 in the HSK group and 0.696 ±0.064 the control group This difference was statistically significant (p=0.02). The Strehl ratio was statistically lower in the HSK group compared with the control group (0.52±0.030 and 0.61±0.013, respectively, p=0.02) (table 2).

In the HSK group, the mean RMS was higher, but not significantly, in eyes with peripheral corneal opacities than in eyes with a completely clear cornea (except for trefoil) (2.651 μm and 2.131 μm, respectively, p=0.655 for total aberrations; 1.271 μm and 0.831 μm, respectively, p=0.655 for total HOA; 0.579 μm and 0.259 μm, p=0.055 for coma; 0.449 μm and 0.551 μm, p=0.482 for trefoil; 0.447 μm and 0.266 μm, p=0.655 for tetrafoil; 0.525 μm and 0.229 μm, p=0.655 for spherical aberration). There was a (non-significant) trend towards lower MTF and Strehl ratio, in the HSK group with corneal opacities (MTF: 0.437 vs 0.507, p=0.338; Strehl ratio: 0.22 vs 0.89, p=0.179, respectively), (table 3, figure 2).

DISCUSSION

Wavefront analysis can identify and quantify optical abnormalities that may affect visual quality. Emmetropic and ametropic patients with no eye disease and no history of ocular surgery usually have low magnitudes of HOA, regardless of the type of spherocylindrical ametropia.[9] Wavefront analysis has been previously used to compare visual performance in surgery and cornea pathology.[2 10–14] Jimenez *et al*[15] showed a greater decrease in optical quality in affected eyes after resolution of keratitis in comparison with healthy fellow eyes, regardless of visual acuity. Previous studies have reported 0 LogMAR (or 20/20) visual acuity on routine vision scales does not necessarily ensure optimal visual quality.[16] Some patients with recurrent HSK have normal Snellen acuity in the affected eye, yet they report a decrease in visual quality in various situations (such as scotopic or photopic conditions). Based on these complaints, we studied HOA in both eyes of these patients in order to understand the perceived diminution in visual quality.

An advantage of the current study is that the cohort had strictly unilateral HSK, and the distribution of HOA is symmetrical about the median vertical axis (enantiomorphism) in both eyes of patients without eye disease.[7 17] Hence, we compared the wavefront aberrations in the affected eye with wavefront aberrations of the non-affected fellow eye.

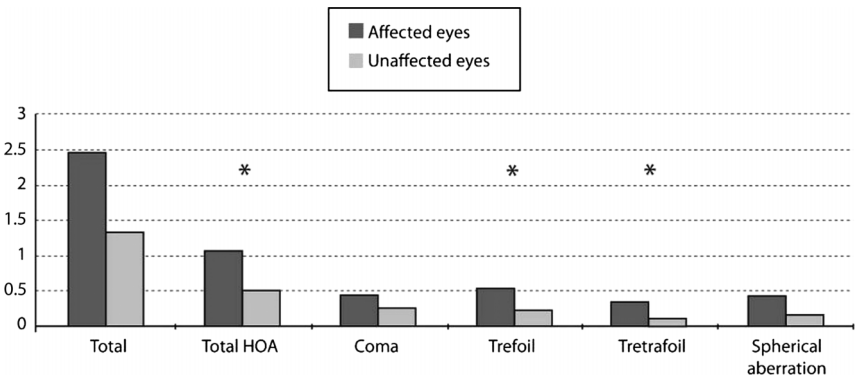

Figure 1 Comparison of root mean square of the various optical aberrations studied in the herpes simplex keratitis group (affected eye) and the unaffected group (unaffected eyes) for the 15 patients.

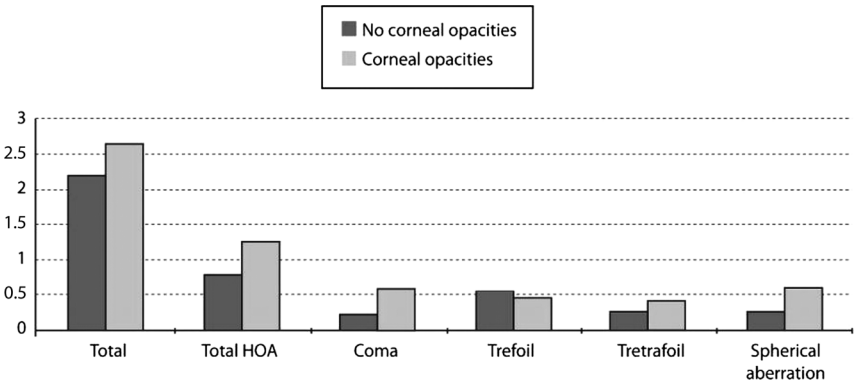

Figure 2 Comparison of the root mean square of the various optical aberrations in the clear cornea group (no opacity) and in the corneal opacities group, for the 15 herpes simplex keratitis-affected eyes.

The actual effect of each HOA on visual quality is still a subject of clinical research. For example, third-order HOAs are known to impact the visual quality.[18] For example, trefoil has been associated with irregular and asymmetrical corneal toricity. Clinically, patients with significant trefoil tend to favour multiple axes of astigmatism during Jackson Cross Cylinder refinement. Tetrafoil, a fourth-order aberration, has also been associated with poor visual quality,[19] responsible for irregular astigmatism that increases in proportion with pupil diameter, and reflects a dephasing of more peripheral points of the wavefront. However, each HOA has a different impact on vision and could interact with other aberrations to influence visual performance.[20] Therefore, it is difficult to speculate on the role of a single HOA as a purely qualitative interpretation of visual function.[21]

Quantifying the optical quality of the eye with metrics such as MTF, PSF and Strehl ratio may reflect an alteration of visual performance due to HOA as a result of the combined effects of all aberrations.[8] These indices are clinically valuable for evaluation of the optical quality of the human eye.[22]

Our results clearly show that recurrent herpes simplex infection of the cornea may induce a significant increase of total HOA, trefoil aberration and tetrafoil aberration. Additionally, we found a decrease in vision quality metrics (ie, MTF, PSF and Strehl ratio) in HSK eyes with apparently good vision despite resolution of an acute recurrence. These results suggest that there are probably infraclinical scars once the acute period seems to have completely recovered. In vivo confocal microscopy has shown that they are important during the acute phase of stromal herpetic keratitis,[23] and some of these histological changes may persist several months after the last acute herpetic relapse.[24] Such changes can alter the optical properties of the corneal stroma, especially the longitudinal organisation of collagen fibres, which is necessary for optimal light transmission. These subclinical abnormalities may explain light-scattering and wavefront abnormalities.

These differences may account for the subjective decrease in visual quality reported by many of these patients which cannot be quantified with standard visual acuity charts. Comparisons of HSV-affected eyes with or without corneal opacities showed an increase in HOA, but the differences were not statistically significant ($p>0.05$). This lack of significance is likely due to the small sample size in each group, leading to insufficient power for the comparison. Despite the small sample size of these subgroups, there was a statistically significant increase of HOA when the affected corneas were clear on slit-lamp analysis compared with the Control group.

The location and extent of the site of disease, and/or corneal scars, may result in subclinical or different types of HOA. However, the sample size required to demonstrate this influence would be much larger and is beyond the scope this study. Stromal herpetic keratitis is a relatively rare form of all herpetic keratitis[2 3] and, among these cases, patients who recover 'normal' visual acuity (20/20) are rare, especially those with several recurrent episodes.[3 25] Hence, we enrolled a relatively small number of patients in our series. Metrics of tear quality and retinal image quality are associated with a decline in vision that occurs with tear break-up.[26] We did not evaluate the quality of the ocular surface of the patients included in this series. However, the aim of the study was to evaluate alteration of visual quality in patients with herpetic keratitis, beyond the putative mechanisms.

Taken together, our results indicate that recurrent HSK induces an increased rate of HOA and a decline in visual quality indices, such as the MTF and the Strehl ratio, while no apparent visual consequences were detected using the more common visual acuity scales. Despite the relatively small number of patients in our series, these results clearly provide new insights to further understand the alterations in visual quality experienced by patients with HSK despite a 'normal' visual acuity. However, a larger, longitudinal study based on wavefront changes during consecutive acute episodes would more clearly define the natural history of corneal changes due to a HSV infection.

Contributors GK: conception and design, writing the article data collection, data analysis and interpretation and literature search (category 1). NP: conception and design and data collection (category 1). MM: statistical expertise, administrative and technical or material support (category 3). IDM and RL: critical revision of the manuscript (category 2). EB: statistical analysis and administrative, technical or material support (category 3). ML: conception and design, data analysis and interpretation, provision of materials, patients or resources, final approval of the article (category 1).

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Patient consent Obtained.

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