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Retroillumination photography analysis enhances clinical definition of severe Fuchs Corneal Dystrophy

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Abstract

Purpose—Retroillumination photography analysis (RPA) provides objective assessment of the number and distribution of guttae in Fuchs Corneal Dystrophy. Here, we assess its correlation with clinical grading using slit-lamp biomicroscopy across varying levels of severity.

Methods—Retroillumination photographs were conducted of 95 affected corneas with slit-lamp flash photography after pupillary dilation. Individual guttae were counted manually and the position of individual points recorded. Clinical grading using the Krachmer scale was documented for each eye during examination, and regression analyses were performed to identify the strength of association with number of guttae. We assessed range at each stage of clinical grading, and utilized the Mann-Whitney U test to assess whether clinical grading levels demonstrated successively higher numbers of guttae.

Results—Krachmer score ranged from 1 to 5, with mean of 2.6. Mean numbers of guttae at each level of severity were 289 (1+), 999 (2+), 2669 (3+), 5474 (4+), and 7133 (5+). Each stage demonstrated significantly higher numbers of guttae than its preceding level except from 4+ to 5+ ($p=0.30$), consistent with the definition of 4+ as the highest level defined by presence of guttae. Higher levels of clinical grading were associated with larger ranges of guttae ($p<0.01$). A linear regression model resulted in a strong fit between RPA and Krachmer score ($r=0.81$).

Conclusion—In this largest study of RPA data and comparison with subjective clinical grading of FCD severity, RPA correlates strongly and demonstrates enhanced definition of severity at advanced stages of disease.

Keywords

retroillumination photography; Fuchs Dystrophy; cornea

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INTRODUCTION

Fuchs Corneal Dystrophy is a progressive, hereditary condition which results in formation of excrescences of Descemet membrane, termed guttae, and development of corneal edema.

Clinical assessment of severity is widely conducted through slit-lamp biomicroscopy utilizing a scale proposed by Krachmer over 30 years ago,¹ which accounts for an increasingly peripheral distribution of guttae over time. Minimal disease is defined as at least 12 central guttae (1+) and extends to stromal or epithelial edema (5+), with scores from 2 to 4 based on concentric diameters of confluent guttae, increasing in size (<2mm, 2 to 5mm, or more than 5mm, respectively).

While widely used clinically for tracking patients over years to decades, the one-to-five scale carries limitations for close monitoring of Fuchs dystrophy. Studies demonstrate that corneal thickness gradually increases across all stages of severity,² suggesting that stromal edema is not specific to end-stage disease. In addition, preclinical disease (5-12 guttae) correlates with FCD-associated genetic variants,³ suggesting value to assessment of trace or subclinical disease. Additionally, interrater reliability is limited with subjective clinical grading, necessitating an objective tool for assessment of severity.

Retroillumination photography (Figure 1) can document formation of new guttae over time,⁴ and summation of guttae in images correlates with specific genotypes of Fuchs dystrophy.^{5,6} We have previously utilized this technique to identify a predominantly inferotemporal distribution of guttae,⁵ a characteristic confirmed with specular microscopy.⁷

In this largest study of retroillumination photography analyses (RPA) for Fuchs dystrophy, we assess its use across the clinical spectrum of severity and demonstrate its ability to define levels of advanced Fuchs dystrophy.

MATERIALS AND METHODS

Selection

We acquired 100 consecutive retroillumination images from individuals with Fuchs dystrophy, of which 95 images were from eyes with clinically significant disease (1+ grading or higher) and were analyzed. A total of 42 individuals were examined; in eight cases, two sets of images were acquired at visits approximately two to three years apart. All patients were examined at time of photography by an anterior segment specialist (AOE or JDG).

The study protocol was approved by the Joint Committee on Clinical Investigation at Johns Hopkins University School of Medicine and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed written consent was obtained from all participants after explanation of the nature and potential consequences of the study.

Image Capture

Retroillumination photographs were acquired as previously described.⁵ Briefly, participants underwent pupillary dilation with a single drop of 1% tropicamide and 2.5% phenylephrine in each eye. We utilized a photo slit lamp (Carl Zeiss Meditec, Dublin, CA) and digital camera (D2xs; Nikon Corporation, Tokyo, Japan) equipped with a magnification changer. The flash power averaged 460 W (range, 240–720 W), and camera aperture was set between f32 and f44. Images captured were displayed on a computer screen in real time to ensure appropriate focus on the corneal endothelium and saved as a 4288 × 2848 PNG file.

A minimum of four photographs was acquired for each eye, with light entering the eye twice on each side. The clearest image from each side was selected for analysis; if two images were equally well-focused, then the image with the smallest shadow was selected.

Hemispheres from each side were then aligned by overlapping corresponding patterns of guttae in each image.

Severity Grading

Clinical grading using the Krachmer scale was documented for each eye at time of examination. Examples of retroillumination images for each level of grading are illustrated in Figure 1.

A single examiner among a team of four medical students evaluated each photograph. Images were imported into Adobe Photoshop software and for each eye, two images were aligned based on patterns of guttae, one with light entering on each side. The hemispheres without a light reflex were joined together at midline (Figure 2). A grid was placed on the center of the image to guide counting and each individual gutta counted using Adobe Photoshop software counting tools, which documents the position of each gutta.

Data analyses

Data were exported from Adobe Photoshop and entered into Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). Regression analyses were performed to identify the best-fit correlation model between Krachmer grading and retroillumination. Ranges of guttae were assessed at each stage of clinical grading.

Mean and median number of guttae were calculated for each level of Krachmer scoring. Given that the distribution of guttae reaches its maximum at level 4 in Krachmer grading (>5mm diameter of confluent guttae; progression to level 5 is dependent on the presence of clinically significant epithelial and/or stromal edema), we sought to understand whether subsets of severity greater than level 4 but without obvious edema could be captured. Therefore, we explored the range at each level of clinical severity.

Non-parametric comparison of consecutive levels was conducted with the Mann-Whitney U test given the non-normative data at each level of severity. ANOVA was conducted to evaluate whether higher levels of Krachmer scores were associated with a higher range of severity. Cases in which severity was documented as a range were included in calculations as the mean score (e.g., “2-3+ guttae” = 2.5).

Pearson correlation coefficient was calculated to determine the strength of association between the two methods of grading. Correlation between eyes was assessed and scores from both eyes of each individual averaged.

RESULTS

A total of 95 corneal images were analyzed. Average Krachmer grading was 2.6, with range from 1+ to 5+ severity. Mean levels of guttae increased with each level of severity, from 135 guttae (Level 1) to 7133 guttae (Level 5), and are demonstrated in Figure 1. Differences between the maximum and minimum number of guttae associated with each level of Krachmer grading were greatest at level 4 (8868 guttae). We compared the number of guttae at each level of severity with its subsequently increased level of severity, and found a significant increase at each level of increased distribution of guttae except from level 4 to 5, which represents the presence of edema rather than an increase in guttae (Table 1).

Correlation between eyes was markedly strong ($r=0.94$). The Pearson correlation coefficient was calculated between grading methods and suggested strong correlation ($r=0.81$) as seen in Figure 3.

The ability to define specific levels of distribution of guttae beyond $>5\text{mm}$ diameter (Level 4 on Krachmer scale) would be expected to result in a higher range of guttae associated with higher levels of severity. ANOVA between Krachmer score and range of guttae at each level demonstrated significant association ($p<0.01$).

DISCUSSION

In this largest study of retroillumination photography for determination of severity in Fuchs Dystrophy, we demonstrate that RPA correlates strongly with clinical grading, and that a high range of severity is captured for patients reaching 4+ in Krachmer grading, the maximum level based on distribution of guttae in this classic method.

Identification of specific levels of severity will be useful for future clinical trials seeking to document rates of disease severity and/or progression. In particular, patients who have reached 4+ severity may continue to develop thousands of guttae before clinically apparent edema is present, the point at which they would progress to 5+ severity. Moreover, the use of subjective clinical grading may be limited by moderate interrater reliability, highlighting the importance of additional objective techniques to determine severity.

In contrast to pachymetry, for which baseline figures vary across persons and races, all individuals with Fuchs Dystrophy begin with a baseline of 0 guttae. Therefore, summation of guttae provides a comparable figure which may be utilized for understanding severity in cross-cultural settings. Future directions include automation of counting of guttae to maximize efficiency of analyses.

Acknowledgments

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Figure 1.
Sample retroillumination photography images of Fuchs Corneal Dystrophy assessed across various levels of Krachmer grading. Increasing levels of severity are associated with higher numbers and increasingly peripheral distribution of guttae.

Figure 2. Sample post-processing retroillumination image of Fuchs dystrophy. Two hemispheres opposing the light reflex are joined together. These are aligned through the identification and overlapping of common clusters of guttae.

Figure 3.

Krachmer score vs. guttae counted using retroillumination photography analysis. Individual measurements appear in blue, with mean score at each level of Krachmer score in orange. The highest range of guttae for a specific score (8868) is associated with a score of 4+, reflecting the utility of RPA to specifically define severity past a 5mm diameter of confluent guttae. Correlation between methods ($r=0.81$) is strong.

Table 1

Number of guttae at each level of clinical severity, as defined by Krachmer grading. In cases for which patients were documented using a range (i.e. “1-2+ guttae”), calculations were conducted with the mean score (“1.5”). Highest ranges of guttae appear starting with level 4, which corresponds with the maximum score based on distribution (more than 5mm diameter of confluent guttae). For each Krachmer score integer, one-sided Mann-Whitney U test was conducted to assess for an increase from the class of grading one degree below. Significant overlap existed between eyes with 4+ and 5+ grading, consistent with the definition of each level.

Krachmer Score	Mean Guttae	Range	Minimum	Median	Maximum	Number of images	P-value
1.0	135	359	43	95	402	18	
1.5	687	1519	38	586	1557	7	
2.0	850	2720	130	672.5	2850	20	
2.5	1272	1283	699	1008	1982	11	<0.001
3.0	2093	2173	1141	2065	3314	7	
3.5	3173	4585	1251	2843.5	5836	8	<0.001
4.0	5215	8868	1528	3622	10396	11	
4.5	5883	6923	2268	6503	9191	7	<0.01
5.0	7133	7227	3605	7156.5	10832	6	