Laser flare photometry in uveitis

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Abstract:

Aqueous flare and cells are inflammatory parameters of anterior chamber inflammation resulting from disruption of the blood-ocular barrier. The ocular inflammation related to anterior chamber cells and flare is assessed by conventional clinical grading systems through using the slit-lamp examination. However, a more quantitative and objective assessment is needed for more precise and reproducible inflammatory assessment in uveitis. Laser flare photometer (LFP) was introduced as a noninvasive, objective, and quantitative evaluation of aqueous flare intensity and number of cells in the anterior chamber with good accuracy and repeatability. The success of LFP allowed clinicians to further evaluate the pathophysiology of intra-ocular inflammation and to incorporate LFP measurements to their routine clinical practice for diagnosis, management, and treatment of uveitis cases. In this review, we will discuss the importance of clinical utilization of LFP and the correlation between LFP and clinical grading systems along with some technical aspects. Furthermore, we will give a literature summary on the current applications of LFP in clinical practice of cases which present with various types of uveitis and diverse ocular conditions with or without inflammation.

Keywords:

Flare grading, laser flare photometry, uveitis

Introduction

Flare is defined as the reflection of light from proteins in the aqueous humor whose presence is caused by a breakdown of blood-aqueous barrier (BAB) due to ocular inflammation. As the protein count increases in the anterior chamber, the translucency of the aqueous humor decreases and gives the aqueous a cloudy or milky appearance called flare or the Tyndall effect.[1] For assessment of anterior segment inflammation in uveitis, clinicians estimate the concentration of cells in the aqueous humor by counting the number of cells in a specified volume and estimate the amount of protein in the aqueous humor by grading the translucency of the anterior chamber on biomicroscopic examination, hence called "flare grading."

In order to quantify the measures of cells and flare in the anterior chamber, Hogan *et al*.[2] have developed grading systems based on slit-lamp findings. The cell amount is scored from 0+ to 4+ based on the number of cells counted in the slit-lamp beam, while the grading of flare is dependent on the ability to visualize iris and lens details [Table 1]. In 2004, the First International Workshop on Standardization of Uveitis Nomenclature (SUN) was held to standardize terminology and grading systems.[3] The grading system of Hogan *et al*.[2] was adopted with minor modifications for the grading of cells and remained almost the same for the grading of flare. A faint flare is graded as 1+; a moderate flare with clear iris and lens details is graded as 2+; a marked flare with the haziness of iris and lens details is graded as 3+; an intense flare with the presence of fibrin or plastic aqueous is graded as 4+ [Table 2]. This grading system depends on the experience of the observer to interpret the slit-lamp findings. Grading of cells can be considered semi-quantitative because it is based on the number of cells in a fixed field. Grading of flare, however, is qualitative and is subject to intra- and inter-individual variations.[3]

In 1988, Sawa *et al*. introduced the laser flare photometer (LFP), which enabled an objective and quantitative determination of flare intensity and number of cells in the aqueous humor based

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Table 1: Classification for grading anterior chamber cells and flare

Grade	Number of cells	Flare
0	No cells	Complete absence
1+	5-10	Faint (Barely detectable)
2+	10-20	Moderate (clear iris and lens details)
3+	20-50	Marked (Hazy iris and lens details)
4+	>50	

Hogan *et al*.[2]

Table 2: Grading scheme for anterior chamber cells and flare based on standardization of uveitis nomenclature criteria

Grade	Number of cells	Flare
0	1<	None
0.5+	1-5	Nonapplicable
1+	6-15	Faint
2+	16-25	Moderate (clear iris details)
3+	26-50	Marked (Hazy iris details)
4+	>50	İntense (fibrin or plasmoid aqueous)

Jabs *et al*.[3]

on the same principle as slit-lamp microscopy. The LFP device was further developed by KOWA Company, Ltd. (Tokyo, Japan).[4] The instrument is comprised a He–Ne laser beam as the incident light and a photomultiplier as the detector of the intensity of the scattered light, both of which are mounted at an angle of 90 on a slit-lamp microscope, aligned in the anterior chamber. The amount of backscattered light is proportional to the concentration and size of proteins in the aqueous humor. The sampling window size of the photomultiplier is vertical 0.3 mm × horizontal 0.5 mm in the air and positioned in the center of the laser beam. The data obtained are thus analyzed by a computer. For flare measurement, which is generally dependent on the concentration of protein in the anterior chamber, the laser beam is programmed to execute a vertical scan, for a length of 0.6 mm, covering the sampling window. The average of results taken from outside the sampling window, which presents the background signals, is subtracted from the measurement taken from inside the window to detect the flare level. The unit of measurement is photon count per milliseconds (ph/ms). For cell measurement, the laser beam performs a two-dimensional scan within an area of 0.6 mm × 0.25 mm, in a sampling window for 0.5 s. Whenever a peak in a particle exceeded 4 photon counts/400 μs, it is considered a cell and the total number of peaks counted by the computers gives the number of cells in the fixed measured volume.[5]

Validation of flare measurement

Several studies were performed to correlate between aqueous protein concentrations and laser flare measurements,[4,6,7] where LFP values were well correlated with the protein concentrations based on serial dilutions of the protein samples taken from plasma or aqueous humor samples obtained from patients who had intraocular surgery. Additional studies were done to determine the reproducibility and accuracy of the laser flare photometer (LFP). In these studies, ocular inflammation was graded using slit-lamp examination and LFP by experienced observers, with measurement of intra- and interobserver variabilities. The results showed that the measurements are highly reproducible with low intra-and interobserver variations.[8,9]

Factors that affect LFP measurements

Several factors are suspected to have an effect on the amount of flare that is measured by LFP. This might be related either to the change in aqueous protein concentration or the amount of light backscatter from the aqueous humor and/or the anterior segment structures that are involved during measurement.

Flare values tend to increase with age in healthy eyes. The mean flare levels between 20 and 40 years are found between 2.9 and 3.9 ph/ms, increasing to 5.0–6.5 ph/ms in the 8th decade of life. The possible cause is the deterioration of BAB with aging,[10-12] although backscatter from increased lens density might also have an additional effect, which will be discussed below.

Mydriasis has a slight lowering effect on flare values in normal individuals. The lowering effect is suggested to be the increase in the aqueous humor volume, and the increase in cells caused by mydriasis occurs because of the liberation of the pigments of iris, not due to an inflammatory reaction.[12,13] Flare also shows a diurnal variation that is inversely related to the ocular pressure. Findings were considered to represent changes in actual aqueous protein concentration.[14]

The effect of several ocular drugs over LFP readings is given in Table 3.[15] The major drug-related effect occurs as an increase in flare value after usage of anti-glaucomatous medication, which is due to a decrease in aqueous volume and subsequent increase in the aqueous protein concentration.[16-19] Drugs that cause mydriasis, on the other hand, lowers LFP readings due to factors that are given above.

Background light scattering from anterior segment structures can affect the flare measurement. It is well known that backscatter form cataractous lenses has a considerable effect over LFP measurements,[20] although it has been shown that milder light backscatter from a noncataractous anterior cortical lens could also have an additional effect over LFP readings.[21] Iris scatter is also a contributing factor, which could be decreased by mydriasis[1] or proper positioning of the calculation window during LFP acquisition, for the amount of scattering is inversely proportional with the distance to the scattering surface.[22]

Comparison of clinical flare grading with LFP

Many studies comparing photometry readings to clinical grades of flare are based on slit-lamp biomicroscopic examination and standard grading methods, which show that the flare laser photometric values are in correlation with the clinical grading of flare.[4,15,23,24] However, each clinical grade has a large range

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Table 3: Effects of drugs on laser photometry values

Medication	Effect on LFP values	Notes
Acetazolamide	Increase	Approximately 40% increase 2-10 h after administration
Apraclonidine	Increase	Increased at 30 min after instillation and remained elevated at 6 h Maximal elevation was 47%-7%
Epinephrine	No effect	No effect measured from 1-6 h after topical instillation
Latanoprost	No effect	No significant effect observed after 21 days in patients with chronic open-angle glaucoma or pseudoexfoliation syndrome
Mannitol	Increase	Increased 75% in patients 20-22 years old at 1 h after intravenous administration and returned to baseline by 3 h Increased greater than 100% at 1 h in patients aged 55-87 years and returned to baseline by 6 h
Phenylephrine	Decrease	Decreased significantly at 3 h after instillation
Pilocarpine	Increase	Increased by a maximum of 20% at 3, 8, and 10 h after instillation
Timolol	Increase	Increase 2.8-2.4 photon units/msec in patients with chronic open-angle glaucoma or pseudoexfoliation syndrome measured 21 days after starting timolol
Tropicamide	Decrease	Decreased approximately 10%-30% by 30-60 min and remained decreased for as long as 3 h. The effect has been reported in phakic and pseudophakic eyes

Ladas *et al*.[15] LFP: Laser flare photometry

of LFP values and there are overlapping values between clinical grades. Due to incertitude of clinical decision to grade low inflammatory activity, this phenomenon is emphasized for low clinical grades of 0 and 1+, which led to the introduction of intermediary grading steps of 0.5+ and 1.5+ by certain research groups and to establish a modified SUN classification system.[25] The correlation between the original and modified SUN grading systems and LFP measurements was further investigated by a recent study, which showed good agreement among the methods and also proposed LFP cut off values to discriminate consecutive grading levels to reduce the LFP overlap between clinical grading steps.[26] In this perspective, LFP could be used a beneficial tool for clinicians to improve their grading of cases with ocular inflammation.

LFP and Uveitis

Laser flare photometry is considered superior to slit-lamp flare evaluation in cases of intraocular inflammation and uveitis to detect any changes in flare reduction and thus monitoring disease activity.[27] LFP-measured flare has become the only quantifiable parameter for most cases of intraocular inflammation both in anterior and posterior segment inflammation.[28] LFP is a valuable tool to remove observer bias in flare grading and it can be used to regulate treatment doses, as shown in a study where the adoption of LFP-guided treatment has changed the treatment course in 11% of cases.[29]

Human Leukocyte Antigen B27 -B27related anterior uveitis

Acute anterior uveitis (AU) is the most frequent and prevalent form of uveitis, and about half of all patients with AU are human leukocyte antigen B27 (HLA-B27)-positive. HLA-B27-associated acute AU is a distinct clinical entity that has wide-ranging medical significance due to its ocular, systemic, immunologic, and genetic features.[30]

The sensitivity of LFP to detect anterior chamber reaction in HLA-B27-related AU is proven to be a useful and reliable tool in clinical practice. In a study held by Bernasconi *et al*., the sensitivity of laser flare photometry was compared to slit-lamp cell evaluation of patients with AU, which has shown that LFP was significantly more sensitive to detect both 50% ($P = 0.001$) and 90% ($P = 0.02$) flare reduction in assessing the decrease of anterior chamber inflammation. LFP was also superior to slit-lamp cell evaluation in monitoring anterior chamber inflammation in uveitis.[27]

LFP can be used in treatment adjustment, especially in cases that do not respond to topical steroids. In a previous study to detect the inflammatory profile of HLA-B27 AU, LFP was again successful to detect 50% and 90% of flare reduction that occurred after 2 and 8 days, respectively, after using the standard treatment of hourly topical 1% prednisolone given for 3 days and the following treatment adjustment according to the response. In cases that did not show any flare improvement as detected by LFP after 48 h were given periocular steroids and thus improved within 24–48 h.[31]

Fuchs' uveitis syndrome

Fuchs uveitis syndrome is a chronic, typically unilateral, ocular condition characterized by an asymptomatic mild inflammatory syndrome that can result in cataract and secondary glaucoma. Fuchs uveitis syndrome is most likely the result of different insults or pathogenic mechanisms, including infections, autoimmune diseases, hereditary, and sympathetic dysfunction.[32] Eyes with Fuchs' uveitis syndrome tend to have higher flare values (photon count/ms) than the nonaffected fellow eyes, showing a positive correlation with the amount of iris depigmentation and keratic precipitates.[33] However, LFP values are only moderately elevated when compared to other types of AU, and the contralateral unaffected eye has similar LFP values of a healthy eye.[34]

Juvenile idiopathic arthritis -associated uveitis

Juvenile idiopathic arthritis (JIA) is a spectrum of heterogeneous chronic childhood arthritis with onset before the age of 16 years and persisting 6 weeks or longer.[35] The incidence of AU in JIA has been estimated between 3% and 18%.[36] JIA-associated uveitis is a devastating disease that leads to sight-threatening complications including band keratopathy, cataract, synechiae, and glaucoma.[37]

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LFP is used as an important tool in monitoring the course of disease and treatment response in JIA-associated uveitis. In a long-term study held by Orès *et al*., fifty-four patients (87 eyes) were followed for 9.9 ± 5 years in two groups according to the percentage of decrease in LF*P* value between baseline visit and 1 month after anti-inflammatory treatment. Cases with an LFP decrease more than 50% had better visual improvement and less complications than those who had <50% of LFP decrease.[38] Furthermore, the flare level is a prognostic factor regarding outcome of the disease. In a study held by Tappeiner *et al*., higher LF*P* values with a baseline >20 ph/ms were associated with a complicated course of disease with poor vision.[39] The presence of flare even without clinically evident cell in the anterior chamber was found in the presence of certain uveitis complications, for example, posterior synechiae and cystoid macular edema,[40,41] thus making LF*P* value a better prognostic factor for the development of subsequent uveitis complications than anterior chamber cells.[39] LFP showed that patients on minimal treatment and with no active inflammation on slit-lamp examination had improvement in the visual acuity and BAB function after starting maximal treatment therapy. Tugal-Tutkun *et al*. demonstrated in a study that patients with a deleterious evolution and complications were found to have much higher mean initial flare of 184.98 ± 97.04 ph/ms with a suboptimal reduction of flare values to 106.1 ± 82.31 ph/ms (42.5% reduction) after maximal treatment, as compared with the group with a favorable outcome whose initial flare was much lower (69.81 ± 89.64 ph/ms) and who responded well to maximal therapy with a reduction of flare to 24.94 ± 21.37 ph/ms (65% reduction). Thus, the initial flare value is found to be a strong predictor of disease course and severity.[1] A residual flare that remains after maximal therapy indicates a permanent breakdown of BAB.[42]

Behçet's disease

Behçet's disease is a chronic, relapsing, inflammatory disease of unknown etiology with unpredictable exacerbations and remissions. First described in 1937 by the Turkish dermatologist Hulusi Behçet as a triad (oral and genital ulcers and uveitis), it is now recognized as a multisystemic disease.[43]

One of the earliest studies to detect the values of LFP to quantify and monitor inflammation in patients with posterior uveitis of different etiologies was done by Guex-Crosier *et al*.[44] The study included four patients with Behçet disease where there was a significant decrease in flare after initiation of systemic treatment. It was also reported that whenever the flare value increased 20% from the lowest value, it was followed by a recurrence of disease.[44]

In a large series of patients with Behçet's disease, Tugal-Tutkun *et al*. demonstrated the utility of LFP.[45] The study had 73 patients without ocular involvement, 54 Behçet's disease patients with acute uveitis attack, and 53 patients with clinical remission for at least 3 months. Patients with no ocular involvement did not have any subclinical flare increase, while the mean flare in patients with remission was shown to be significantly higher than in healthy controls (6.8 ± 4.2 vs. 3.7 ± 0.7 ph/ms). Flare levels had a significant correlation with the grade of aqueous cells at the slit lamp, vitreous haze, and the number of active fundus lesions as well as leakage on fluorescein angiography (FA). It is suggested that the usage of LFP might decrease the necessity to perform fundus FA in monitoring disease activity during clinically quiescent periods. Another important observation is that flare values higher than 6 ph/ms were associated with a significantly higher risk of recurrent uveitis attacks in patients with Behçet disease.[1,45]

In a recent study done by Yalcindag *et al*. to evaluate the association between intraocular inflammation and laser flare photometry measurements in Behçet's disease, the flare levels were compared with the grade of anterior chamber cells, the presence of vitreous cells, the complications of uveitis, and FA scores. The median flare levels were 8.4 (6.67–16.47) ph/ms in the attack group, 4.85 (3.85–10.62) ph/ms in the remission group, and 2.8 (2.35–4.83) ph/ms in the healthy controls. With the attack group having the highest flare intensity, the flare levels were both higher in uveitis groups compared with healthy controls. The flare levels were correlated to the grade of the anterior chamber cells, the presence of vitreous cells, and the FA findings. As anterior chamber flare measured by LFP showed a strong correlation with clinical findings and FA leakage score in Behçet patients, it can reduce the necessity of FA for monitoring subclinical inflammation during clinically quiescent periods and may be an indicator of posterior segment activity when FA is not applicable.[43]

Vogt-koyanagi-harada disease

Vogt-Koyanagi-Harada (VKH) disease is defined as a bilateral granulomatous panuveitis with or without extraocular manifestations affecting young adults. It is most likely a T-cell-mediated autoimmune reaction against one or more antigens associated with melanocytes, melanin, and retinal pigment epithelium.[46]

The clinical application of LFP in VKH patients is assessed by multiple studies. In a prospective study done by Fang *et al*. LFP was used to quantitatively evaluate the changes of aqueous flare and cells in eyes with VKH disease. The study included 35 initial-onset VKH patients (70 eyes) and 46 recurrent VKH patients (92 eyes) following immunotherapy. The mean flare value was significantly higher in the recurrent group than in the initial-onset patients before treatment (43.6 ± 20.7 vs. 8.1 ± 4.1 ph/ms) as well as 2 weeks and 1, 3, and 6 months after treatment. The mean cell count was also higher in the recurrent group in the pre- and posttreatment duration. Based on this study, it was concluded that recurrent VKH patients displayed a more striking and long-lasting breakdown of the BAB and more severe inflammation than initial onset patients, and BAB lasted longer than aqueous cells in both forms of the disease.[47]

In retrospective case series done by Maruyama, *et al*.[48] to study predictors of recurrence in patients with VKH disease, patients with recurrent attacks of inflammation were classified

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as recurrent, whereas patients needing only steroid treatment, without any recurrent attacks, were classified as nonrecurrent. Flare in the anterior chamber was measured in these patients using LFP. Patients with recurrence had higher initial flare value and lower visual acuity than patients with nonrecurrent VKH disease. Therefore, visual acuity and LFP levels during the initial phase may be useful as prognostic factors to monitor VKH disease and to evaluate therapeutic options.

In a recent study designed to evaluate underlying subclinical ocular inflammation in VKH disease with sunset glow fundus (SGF), clinical records of 34 eyes of 17 VKH patients with SGF including laser flare photometry (LFP), enhanced depth imaging optical coherence tomography, and indocyanine green angiography (ICGA) were reviewed.[49] Inflammatory signs were detected in 23 out of 34 eyes by LFP (67.6%) and active inflammatory signs detected by ICGA were also observed in 77.8% of the eyes by LFP. In addition, positive flare count was the significant prognostic factor of positive ICGA score with odds ratio 11.7. Thus, LFP can be a useful tool that helps in the monitoring of cases with chronic VKH.

Other ocular disorders

Because of the sensitivity and accuracy of laser flare photometry to detect alterations of the blood-ocular barriers, it is increasingly used to study the effect of any procedure or intervention on postoperative inflammation.[1] Laser flare photometry allowed comparison between different surgical techniques, surgical adjuncts, and anti-inflammatory medications.[50-57] A study held by de Maria *et al*. evaluating the persistency of anterior chamber flare with LFP after uneventful phacoemulsification in asymptomatic patients with no signs of inflammation on slit-lamp examination, the author showed that persistent anterior chamber inflammation can persist in a significant number of uncomplicated cataract cases for a long amount of duration after cataract surgery and may be responsible for late-onset cystoid macular edema.[58] LFP can also be used for the detection of the risk of PVR in vitrectomy cases. Conart *et al*. demonstrated in a study on 100 eyes that preoperative aqueous flare is a strong predictive factor for PVR-related re-detachment of the retina.[59]

Laser flare photometry studies have shown an increase in aqueous flare values in a variety of noninflammatory posterior segment disorders such as diabetic retinopathy, retinal vein occlusion, retinitis pigmentosa, and choroidal melanoma.[60-63] Miyake *et al*. reported that laser flare photometry values were higher in patients with central retinal vein occlusion (CRVO) than in those with branch retinal vein occlusion. In addition, the flare values were significantly higher in hemorrhagic CRVO when compared to those with venous stasis alone.[64]

Conclusion

Laser flare photometry represents the first noninvasive, objective, and quantitative method for the determination of the BAB functions and thus assessing intraocular inflammation. It allows a quantitative flare evaluation that cannot be measured with normal slip lamp examination with a good repeatability. Current research proved the standard role of LFP in monitoring and assessing intraocular inflammation and its use to adjust treatment modalities, making it an indispensable tool in the uveitis clinic. Ongoing studies are evaluating its role in fields different than uveitis such as cataract and vitreoretinal surgery. Future studies hold more possibilities for the use of laser flare photometry and to confirm it as an irreplaceable tool in uveitis practice.

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Conflicts of interest

There are no conflicts of interest.

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